Section of the History of Medicine

President K D Keele MD

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Paper

King Charles I and William Harvey

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WILLIAM HARVEY

On May 13, 1960, about a fortnight before his death, John Fulton, Sterling Professor at Yale University, wrote thanking me for letting him see the epilogue to a Life of Harvey which I had written, and hoping that it would be printed without change. He also said that the idea of Harvey and King Charles I being a 'Royal Society' in embryo was a charming one, and how appropriate for the Tercentenary Year! To copy Dr George Ent in his 'Epistle dedicatory' to 'De generatione animalium', 'You have thus, Gentlemen, the reason for this address'.

Miss C V Wedgwood, in her book 'Seventeenth-Century English Literature' (1956), wrote:

'Our ancestors in 1600 were unlike us in many ways. The phlegmatic Englishman had not yet become an established type. In 1600 the English were a lively, excitable, high-spirited people, expressing themselves spontaneously in song and rhyme, exclamation and gesture. They enjoyed acting, mumming, mimicry, country dances and round games, of which they had an unconscionable number, "barley-break", "John, come kiss me now", "hot cockles", "handy-dandy", "leap candle", and "fair and softly passeth Lent".... With all the danger and the cruelty, the poverty and the pain, English life seems to have had the colour and the irrepressible gaiety now only found in warmer climates.'

The picture of an active, high-spirited people is not too dissimilar from Aubrey's description of Harvey as 'short of stature, dark of skin, with shining black eyes and hair, alert and irritable, often fingering the handle of his dagger'. It also seems to fit one who could produce the passage introduced into Ch.V of 'De motu cordis et sanguinis', with consequent increase in tempo. This passage reads, 'This is comparable with what happens in machines in which, with one wheel moving another, all seem to be moving at once. It also recalls that mechanical device fitted to firearms in which, on pressure to a trigger, a flint falls and strikes and advances the steel, a spark is evolved and falls upon the powder, the powder is fired and the flame leaps inside and spreads, and the ball flies out and enters the target' (Harvey 1957). The passage as a whole has the rapid sequence which Demosthenes from time to time secured in his speeches by the deliberate introduction of a couple or so of hexameters, and I see in it one of a number of examples of Harvey's dynamic personality coming through into the very words with which he continued his unremitting efforts to convince his contemporaries of the truth which he had found.

William Harvey (1578–1657), whom I have called in the script of the new edition of 'A Short History of Physiology', 'last of the ancients', 'first of the moderns', 'the definer and founder of experimental physiology', was the son of Thomas Harvey (1549 or, on C J Sisson's finding, 1551–1623) and of his second wife and was born at Folkestone on April 1, 1578, qualifying thus to be styled an Elizabethan.

During the summer of 1588 he passed the examination in reading, writing, English and Latin before his admission into Canterbury Grammar School (or King's School, Canterbury) as a fee-paying scholar, which admission took place when he was 10 years of age. In the vale of Folkestone he found his kinship with the life of the countryside, a not unimportant point, for natural historians of his ability tend to be born, not made.

In his 16th year he entered Gonville and Caius College, Cambridge, where he was the only one of the first ten holders of the Matthew Parker Scholarship eventually to take up medicine, though the conditions of the Scholarship were most favourable, namely, three years of subjects ancillary to medicine, followed by three years of medicine itself. Further, the students had to be able, learned and worthy youths born in Kent and educated at Canterbury and, in Harvey's case, it was the first instance of a scholarship for medical training (Herringham 1932, p. 111).

He kept his residence well at Caius up to the summer of 1596, but after that he had many and prolonged absences, some of them due to ill-health. He finally left Cambridge on October 30, 1599, intending to return in January 1600 but the first part of that year found him instead at Padua, where he not only had the good fortune to be a pupil of the great Hieronymus Fabricius of Aquapendente, but finally on April 25, 1602, graduated as Doctor of Medicine of the University of Padua. He stayed on in that city until perhaps August, but returned fairly soon to Cambridge to incorporate there as Doctor in the same faculty. For, though the Paduan degree allowed him to practise in England, he needed the *ad eundem* one to become eligible in time for the Fellowship of the College of Physicians, and all his planning-ahead was always consummately well done. In recalling in 1662 Harvey's life at Cambridge, Scarburgh (Payne 1957) told of

'the great goodwill, the esteem and the devotion which he excited among those around him . . .

'He devoted himself assiduously to his studies and turned with the greatest zeal to philosophy. After the manner of the ancient philosophers (as they say about Plato and Pythagoras) he thought that he should travel as widely as possible in the hope of acquiring thereby some of their teaching and wisdom. Therefore this genius did not continue to remain in this country [i.e. England]. It seems that while he studied at Padua, and not before, Harvey began to think of his career. He thought again and again and for a long time how he could raise himself effectively from the ground and place his head among the stars and at last there settled in his mind the wish to embrace medicine', in which his subsequent progress was breathtakingly rapid.

After his incorporation as MD of Cambridge in 1602, Harvey lost no time in applying for admission to the College of Physicians, his first appearance being on May 4, 1603, and he was finally admitted a Candidate on October 5, 1604; a month or so later he married in St Sepulchre's Church, Holborn, Elizabeth Browne, daughter of Dr Lancelot Browne who had been first physician to HM Queen Elizabeth I. He was elected Fellow on May 16, 1607 (Barlow 1916), and began an active association with the College that ended only with his death. In 1608 he brought to the Governors of St Bartholomew's Hospital letters of recommendation from King James I, on receipt of which these Governors loyally elected him Physician in reversion or, as one would now say, Assistant Physician.

In 1652 and, therefore, during Harvey's lifetime, Henry Power (1626–1688) wrote of 'Circulatio harveiana inventa ab authore A.D. 1614'.[1]

[1]Henry Power left the B.M. MS Sloan (1345) written in 1652, and therefore during Harvey's lifetime, with a section entitled 'Circulatio harveiana inventa ab authore A.D. 1614'. Power's MS therefore antedates by two years the earliest known reference to the Harveian circulation of the blood (*see* Rolleston 1928).

Harvey was in 1615, in fact, appointed to the Lumley and Caldwell Lectureships on Anatomy and Surgery in the College of Physicians, and he gave three lectures on April 16, 17 and 18, 1616. In the second one he stated, according to the Latin-English mélange which he used in 'Prælectiones Anatomiæ Universalis',

> W. H. constat per fabricam cordis sanguinem
> per pulmones in Aortam perpetuo
> transferri, as by two clacks of a
> water bellows to rayse water
> constat per ligaturam transitum sanguinis
> ab arterijs ad venas
> unde △ perpetuum sanguinis motum
> in circulo fieri pulsu cordis.

(W. H. shows that blood is carried continuously through the lungs to the aorta by way of the heart mass as by two clacks of a water bellows to raise water. He shows by means of a ligature that the blood passes from the arteries to the veins and thereby demonstrates that the movement of the blood is a circular one caused by the heart beat. – Harvey 1886.)

From 1616 to 1628 there were no objections at the College of Physicians to Harvey's revolutionary new ideas except on the part of Dr James Primrose, who accepted Galen as authoritative, one of his arguments being that in the olden days patients were healed without a knowledge of the circulation and that therefore this doctrine, even if true, would be useless.

In February 1618 Harvey was appointed Physician to King James I, and in March 1625 he attended him in his last illness.

In 1628, the year in which he turned 50 and King Charles I 28, Harvey was elected Treasurer of the College of Physicians and also published his first book, entitled 'Exercitatio anatomica de motu cordis et sanguinis in animalibus' (An anatomical exercise on the movement of the heart and blood in animals), the English publisher of the book having probably been suggested by Harvey's friend, Robert Fludd, or Robert de Fluctibus. So William Fitzer, of Frankfurt, received what has been described as 'the most important medical work ever written', for it contained Harvey's 'new concept of the heart's movement and function and of the blood's passage round the body'. In demonstrating this, in Hoffmann's phrase, he had surely shown the world 'the truth that is more beautiful than the evening and the morning stars' and had raised himself effectively from the ground and had placed his head among the stars, as he had planned to do during his student days at Padua.

In 1631 he became Physician to King Charles I and to the Royal Household, and it is probable that, after that appointment (Paget 1846), the greater part of his time was spent with the Court.

From the date of the surrender of Oxford (July 1646), where for a while from April 1645

Harvey had been Warden of Merton College (Fig 1) he followed the fortunes of Charles no longer. Of his reasons for quitting the services of his master of a generation we know nothing (Willis 1847); at 68, which was Harvey's age, a man begins to feel that an easy chair is a fitter resting-place than the bare ground, a ceiled roof more suitable covering than the open sky – prospects which a continuance of the struggle held out. Harvey, besides, had no stomach for contention in any shape or form, not even in the literary arena; and he now probably resolved to follow the advice he had once given to his young friend Charles Scarburgh 'to leave off gunning and dedicate himself wholly to more congenial pursuits'.

Towards 1636 King Charles I had decided to send to Ratisbon an embassy of such weight and importance that a definite decision about the intentions of the Emperor Ferdinand II with regard to the Palatinate could scarcely be withheld. It was to be headed by the Earl of Arundel, who went to Court sometimes, it was said, because there only was a man greater than himself, and went there the seldomer because there was. The Embassy left Greenwich on April 7, and landed at Deal *en route* back to London on December 27. One of the letters sent by Harvey, who accompanied the Embassy in a medical capacity, to Lord Feilding said that he, Harvey, would be glad of any occasion to see Venis [Venice], though maybe he had visited it in 1600–1602 while at Padua. More interesting is the fact that they reached Nuremberg, not far from the University of Altdorf, where Caspar Hoffmann (1572-1648) (Fig 2), who had been a fellow-student of

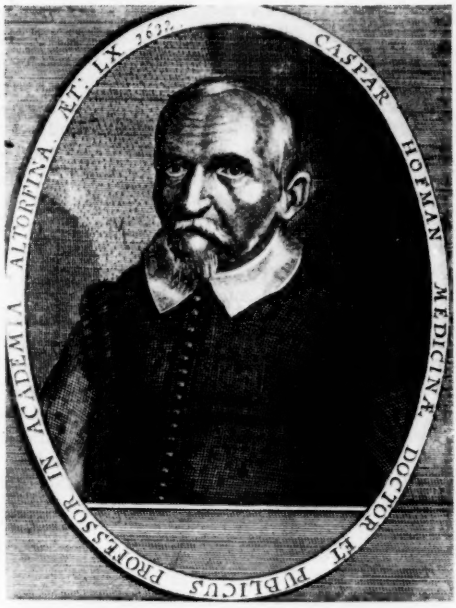

Fig 2 *Reproduction of a drawing of Caspar Hoffmann (1572–1648), Professor of Medicine at Altdorf, Germany, at the age of 60. (Courtesy of the Director, the Wellcome Historical Medical Museum)*

Harvey's at Padua, was Professor. And more remarkable is the fact commented on by Baier in 1728 (*see* Ferrario *et al.* 1960) and again by Richard Landau in 1902, but apparently overlooked thereafter, that in April 1622 the idea of a circulation of the blood had been proposed to Hoffmann by his own pupil Helvicus Dieterich (1601–1655). The occasion was a public disputation at which Dieterich was defending a thesis on the function of the brain. 'In more than one vivisection of a dog he carried out, as physicians still living would testify, almost the identical experiment by which, not long afterwards, the learned Harvey taught the whole medical world the movement and circulation of the blood'. But Hoffmann replied with only his customary 'Pah', together with his wisecrack:

Fig 1 *A 1772 engraving of Merton College, Oxford, of which Harvey was admitted Warden on April 9, 1645*

'You don't want to become a circulator, do you?' One of the most interesting new facts revealed in Harvey's newly-discovered letter to Hoffmann is his statement that there were English anatomists who did not hesitate to say that Harvey had taken his ideas of the circulation from Hoffmann and that he, Harvey, had had to produce his letters and to show the dates in order to refute the charges (Ferrario *et al.* 1960).

In 1649 (the year in which King Charles I was beheaded) Harvey published two essays in reply to the elegant little work by Jean Riolan, jr, entitled 'Encheiridium anatomicum et pathologicum' (An anatomical and pathological handbook) (Riolanus 1649). In status and in his official Court appointment Riolan had been very comparable with Harvey, and the latter's reply is of interest as the only published one which he deigned to make in furtherance of his 'De motu cordis' on what he very happily styled its birthday.

Although the beginning of the Medical School at Harvey's Hospital of St Bartholomew is not recorded, it appears that in 1662 students were in the habit of attending the medical and surgical practice of that Hospital, and that their studies were assisted, five years after the date mentioned, by the formation of a Library 'for the use of the Governors and young University Scholars' (Handbook for the Sessions 1959–1960).

It is, therefore, of considerable interest to learn what Harvey, the innovator, wrote in the first of his two essays to Riolan, for amongst other things he defined our subject in a masterly way.

'The contemplation', he said, 'of those things which are normal is physiology, and it is the first thing to be learned by medical men. For that which is normal is right and serves as a criterion for both itself and the abnormal. By defining in its light departures from it and unnatural reactions, pathology becomes more clearly obvious for the future, and from pathology the practice and art of therapeutics, and opportunities for discovering multiple new remedies, derive' (Franklin 1958).

KING CHARLES I

King Charles the First was born in 1600; he obviously suffered from rickets which, though prevalent in England before the seventeenth century, was first generally recognized between 1620 and 1630 (Parsons 1950). I shall quote at some length from Hilaire Belloc's 'Charles the First King of England' (1933).

King James VI of Scotland was keen to succeed to the English throne, and set off on receipt of the news of Queen Elizabeth's death, brought by one Robert Carey and relays of horses in very short time from London to Holyrood.

There was astonishment and not a little disgust at the first shock of James' appearance, his almost incomprehensible Scottish accent, and his pompous assertive manner which went ill with his lumbering frame and his uncouth face and uneasy glance. The children were left behind; the vigorous young Henry, now 9 years old; Elizabeth, who was 6½; and baby Charles. Later Henry and Elizabeth went south to join their parents, but Charles was left behind, secluded in Dunfermline, where everything was done to foster his constantly failing health and his apparently doomed little weak body, but he lacked companionship. It was not until 1604 that the physicians thought that he could, at some risk, be moved, and the little child was brought down south with every precaution, slowly, stage by stage, to meet his parents.

James loved his children; he was anxious to see baby Charles again; he came out a long way to meet him, even as far as Northampton, and there took the poor little thing up in his arms and raised it and sat it down again, certainly noting – for though his gaze was uncouth and clumsy, he was sharp as a ferret to note what was going on about him – the ill-effect produced by that unhappy morsel of humanity upon the women and even the men of the Court about him. But, fortunately, one Lady Carey took charge of him. James, alarmed at the way in which the months went by, and the child was not able to walk properly though in his fifth year, wanted to have set on either side of his legs those irons which are sometimes used for strengthening children so afflicted. But Lady Carey would have nothing of irons; she believed that Nature would set things right, and Nature, approving of her determination and judgment, obeyed her commands – as did James. But there was yet another affliction – one that Charles never wholly grew out of, although he grew out of all the others, and this was his difficulty in speech.

He was naturally very nervous, and his hesitation was increased by the way he had been kept apart; but the impediment in his speech was also a definite mechanical thing. James was for having a slight operation performed and the ligament at the base of his tongue cut, as is sometimes done in these circumstances. Again, Lady Carey would have none of it. And she carried her point – as indeed she carried all her points, for she was of that kind. And it is to her, and her ability of thus having her own way, that we owe the life of Charles and the many years with which his own character quite as much as his tragedy ennobled the history of England. She also saw that he was kept as much as possible in the country, saving him from the fret and excitement of the Court. When, however, he was a few weeks over 5 years, her rule had to be relaxed for the ceremony of his Duchy. He was carried by peers summoned for that office into the old vast Hall of the Palace of Whitehall, and there had been enough and too much excitement. That was certainly a day he remembered, when he sat there solemnly silent at the head of the table on his high chair, all blazing with jewels. They made him understand when he went to bed that night that he was Duke of York. It was his first touch of grandeur.

He was 11 before he was sufficiently developed for Lady Carey to terminate her charge, but already he

was upstanding and his little body was saved. He might have continued slowly maturing and reluctant to impress himself upon his surroundings, had there not fallen on his family in the next year – just at the end of his twelfth – a blow which changed all things, the sudden death of the beloved handsome elder brother, Henry, on November 6, 1612. And suddenly Charles stood under new stars as heir to the throne. His whole position had changed, his whole meaning to those about him had changed, but the boy, still quite young, too young for his age, and always shrinking too much from contact, knew bitterly enough in what he was deficient, and very young as he was, had begun to determine the strengthening of himself, beginning with an industrious resolve to redeem his body. Being already very short in stature and slight, he would remain so; since he stammered and was ashamed of it, his face fell before the gaze of others; he could still remember how in childhood his limbs could hardly support him. Now, he methodically took to exercise, and with the athletic example of his late brother, whom he had so much admired, before him, he was especially determined to be a good rider. As he was short and weak in the legs, and knew himself to be timid withal, riding the great horse (distinguished in those days from the hackney, and involving much more strength, skill and courage) would be the last thing in the world one would expect him to undertake. Yet, before three years had passed, when he was 15, his ungainly father was surprised and delighted to see the little figure graceful, well set, and controlling from its high saddle the big, mettlesome mount on which it rode. This horsemanship, acquired so early by strength of will, Charles retained to the end. He rode, sitting loosely but well, all his life, and we must remember him as a horseman.

The success of the various efforts at Charles' upbringing is shown in a letter from the Venetian ambassador in London (Huxley 1959) to the Doge of Venice when the Prince was 21.

'The Prince', he wrote, 'has developed with his years, has a truly royal presence, a grave brow, and much grace in his eyes and in the movements of his body, showing a prudent temperance. Such qualities make him more than a Prince, just as his qualities and mind surpass his age. His admirable opinions and customs earn him the universal goodwill and affection of the people. . . . He, as one born to command, seems to scorn obedience to lust and the vices, his self-control at his age causing amazement. He shows no immoderate or vast appetites, but stands fast to virtue, either subduing or not feeling the sensual promptings. So far as one knows, he has not tasted certain youthful pleasures and apparently has not felt love except to some show of poetry; he even blushes like a modest maiden if he hears any scandalous conversation, so the women do not tempt him as they did his brother . . . In all corporal exercises he is admirable. He excels at tilting and indulges in every other kind of horsemanship . . . His only defect some impediment through the size and length of his tongue which prevent him expressing himself freely.'

Charles' household presented a great contrast to the disorderly confusion and lavish extravagance of his father's. He was, the Venetian ambassador wrote, 'methodical and most regular in his affairs, and, in the conduct of his household, wishes to manage everything economically. He wishes his servants to be paid justly and at the proper times, but not to bother him with their demands. Of his own accord he gladly procures for them advantages and honours.'

Bearing upon the Prince's habits of exercise is a passage found in 'Oriel College Records' (Shadwell & Salter 1926), which states that a tennis court, probably the best in Oxford, belonging to the College, was patronized by the King and Prince Rupert in 1642. On January 8 of which year the King wrote 'to his trusty and well-beloved the Provost and Fellowes' desiring them to lend all their plate to him for melting down at his recently opened mint in Oxford. I am glad, however, to say that they retained the so-called 'Founders' Cup', a mazer bowl, and Bishop Carpenter's coconut cup.

No alumnus of Oriel – so close to Merton College – can fail to retain among his Oxford memories the fact that the King in 1645 named Harvey Warden of that College. And no one living in the Oxfordshire village of Yarnton, as I have done since my retirement, is unaware that it was on the route taken by the King on June 3, 1644, in the famous night ride in which he slipped past two Parliamentary armies, by a very skilful manœuvre, with 3,000 horse and 2,500 foot to Handborough Bridge, spanning the Evenlode.

Aubrey is quoted in Arthur M Hind's book (1922) on Wenceslaus Hollar, the artist, as adding a curious little personal reminiscence showing the foreign artist's view of the sour English faces of the Commonwealth. 'I remember he told me that when he first came into England [in 1636], which was a serene time of peace, the people, both poor and rich, did looke cheerfully; but at his returne [in 1652] he found the countenances of the people all changed, melancholy, spightfull, as if bewitched.'

It is not for me to take sides in a long-past Cavalier-versus-Roundhead conflict, but it seems to me that the King was quite illegally, on January 30, 1649, put to death by the severing of his head from his body. Mr Dickson Wright last May showed me two pictures of executions, one being a Dutch cartoon of King Charles' beheading, the other a photograph of a beheading in Bangkok in 1925. 'In both', wrote Mr Dickson Wright, 'you will see the phenomenon of the carotids and the vertebrals spouting into the air, which should have led to the discovery of the circulation of the blood sooner than 1616.'

Fig 3 *An etching by Wenceslaus Hollar of a painting by Van Dyck of King Charles I*

Fig 4 *From Sir Henry Halford's account of 1813, giving 'a faithful representation of the countenance of the King [Charles I] at that time (1813)'*

Interment of the King's Body

Sir Thomas Herbert (who was not knighted until the Restoration) was a Parliamentarian by conviction, was appointed Groom of the Bedchamber, and was a constant guardian and faithful companion of the King from the time he left the Isle of Wight until his death, being thereafter employed to convey the body to Windsor, and to fix upon a place for the interment there. He said that '. . . the sky was serene and clear; but presently it began to snow, and the snow fell so fast, that by that time the corpse came to the west end of the Royal chapel, the black velvet pall was all white (the colour of innocency), being thick covered over with snow . . . Thus went the *white King* to his grave, in the forty-eighth year of his age, and the twenty-second year and the tenth month of his reign.'

'It is not difficult,' wrote Innes-Smith (1959) 'to imagine this sad and dignified scene and to visualize the snow falling upon those few loyal friends bearing the coffin at a "slow and solemn pace" towards St George's Chapel', where the ceremony of interment was a very hasty one, performed in the presence of the Governor as well as of Sir Herbert, the former refusing to allow the use of the service according to the Book of Common Prayer, and leaving repairs to be made later in the Henry VIII vault, which was at the time restored not by regular masonry, but by fragments of stone and bricks, put roughly, and hastily together without cement. Charles' coffin appears also to have injured, by a precipitate introduction, that of King Henry VIII.

That of Charles was re-discovered accidentally through an opening being made, many years later, by a workman, in the walls of the Henry VIII vault and noticing that three, not two, coffins could be seen therein. The Prince Regent was told of the circumstances and, perceiving the need for clarifying a doubtful point in history, ordered an examination to be made at the first convenient opportunity. This was done on April 1, 1813, in the presence of the Prince Regent and others, including Sir Henry Halford Bt GCH PRCP, from whose description of the opening of the coffin the present account is taken (Halford 1831). The vault was situated in the centre of the choir, opposite the eleventh knight's stall, on the sovereign's side. On removal of the pall, a plain lead coffin was seen, which had apparently never been enclosed in wood, and bore an inscription, 'King Charles, 1648', in large, legible letters on a scroll of lead encircling it. A square opening was made in the upper part of the lid, revealing an internal wooden coffin, completely full but very much decayed. When at length the whole face was completely detached from its covering, the forehead and temples were found to have lost little or nothing of their muscular substance; the cartilage of the nose had gone but the left eye, in the first moment of exposure, was open and full, though it vanished almost immediately; and the characteristic pointed beard was perfect. The shape of the face was a long oval, many of the teeth remained and the left ear was found entire. Thus the countenance bore a strong resemblance

to the coins, the busts, and especially to the Van Dyck pictures of King Charles I (Figs 3 and 4).

The head, when completely disengaged from its confining attachments, was found loose and, when taken up and held to view, was quite wet and gave a greenish red tinge to paper and linen which touched it. A portion of the hair, when cleaned and dried, was of a beautiful dark brown colour, that of the beard was of a redder brown. On the back of the head it was over an inch long, and had probably been cut so short for the convenience of the executioner, or to furnish memorials of the unhappy King for pious friends after death.

When the head was held up to examine the place of separation from the body, the muscles of the neck had evidently retracted themselves considerably; and the fourth cervical vertebra was found to be cut through its substance transversely, leaving the surfaces of the divided portions perfectly smooth and even, an appearance which could have been produced only by a heavy blow, inflicted with a very sharp instrument, and which furnished the last proof wanting to identify King Charles the First.

After the head had been examined and served every purpose in view, and without examination of the part below the neck, the coffin was immediately soldered up again, and the vault closed.

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Paper

The Malaria Story

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The early history of malaria is long and confused. Ever since the days of Greece and Rome writers have associated its occurrence in man with proximity to marshes, hence the French term *paludisme*, and the English miasmatic fever. It was left to Albert Freeman Africanus King (1841–1914) to lay down in Washington, in the year 1882, distinct specific facts in favour of this theory and he drew up a list of 19 reasons mostly based on an article by Dr John Metcalfe in 1862 on 'The Nature and Treatment of Miasmatic Fevers' (U.S. San. Comm. Rep.). It was concluded that malaria and mosquitoes were associated with marshes and both were encouraged by turning over the soil.

Almost simultaneously Carlos Juan Finlay (1833–1915) in 1881 in Cuba, postulated that a mosquito (*Aedes ægypti*) could transmit yellow fever from man to man and this was confirmed nineteen years later by Walter Reed and his associates. This did have undoubtedly some effect on current thought about the mode of transmission of malaria.

Discovery

The malaria parasite was discovered in Constantine, Algeria, by Charles Louis Alphonse Laveran on November 8, 1880, and was accurately figured by him in the act of exflagellation. The crescent of the subtertian parasite and associated stages were easily recognizable and named *Oscillaria malariæ*. Although his paper was published in the *Bulletin de la Société Médicale des Hôpitaux de Paris* for December 24, 1880 (**17,** ii, 158), it was a long time before it was generally recognized. Many in fact, including Manson, appear not to have known about it until some ten years later. In 1887 Henry Vandyke Carter (1831–1897) found all the three known types of malaria parasites in India, but he was ignored and ridiculed as a disciple of 'Laverանity'.

It now appears probable that the malaria parasite was seen, although not specifically identified, at an earlier date. Malaria pigment was described by Lancisi in 1716 and by Richard Bright in 1831. H Meckel, 1847, must have been the first to have set eyes upon the parasite itself. R Virchow and F T Frerichs described most certainly what were plasmodia in 1848, and in 1872 Francis Delafield (Professor of Pathology in Belfast) wrote that the most constant finding in malaria was the presence of particles of black pigment in the blood associated with transparent bodies (which obviously were the parasites).

Laveran was fortunate in catching the crescentic form of the subtertian parasite in the act of flagellation for this told him that he was dealing with a living organism. In this respect he was more fortunate than his predecessors who thought that the protoplasmic objects they studied were inanimate (a fact which led to a remark by Patrick Manson, at a later date, 'Had I had the luck of Laveran what a swell I might have been'). The announcement of Laveran was received with scepticism by a public which had often before been fooled.[1]

However, in 1881, Laveran showed two of his preparations in Rome to Marchiafava, Celli, Bastianelli and Golgi, all of whom had more modern and powerful microscopes with oil-immersion lenses and also had at their disposal numerous malarial patients to investigate. Being now convinced and enthusiastic they were able, within the next few years, to describe the various stages of the intracorpuscular parasites and to discern the malaria pigment and the early unpigmented stages. Meanwhile Golgi, in Pavia, in 1885 demonstrated the relationship between the cyclical development of the parasite and the long-known and studied malarial rigors.

In the year 1886 William Osler thrust himself into the picture at the inaugural meeting of the Association of American Physicians in Washington on June 17 and 18, 1886. He attacked a young worker, W T Councilman (1854–1933) who was demonstrating what he thought were Laveran's bodies in the blood of a malarious patient which Osler said were vacuoles in the cell. He was sternly rebuked by G M Sternberg (1847–1919) who exclaimed tartly that if he (Osler) would only stain his films he would be convinced. Osler was so taken aback that he returned to his hospital and postponed his Canadian vacation to search for Laveran's parasite. He *did* find it in October and reported the fact on October 28, 1886, and, when fully converted, he retaliated by publishing his famous *Hæmatozoa of Malaria* in the following year (*see Brit. med. J.*, 1887, i, 556).

Progress

The much-needed stains for the differentiation of parasites came in 1890–1 by the invention by D L Romanowsky, of St Petersburg, of his stain which showed up the parasite and its chromatin for it must be remembered that up till then the only suitable stains were methylene blue and gentian violet. Four years later his colleague, N Sakharoff, demonstrated chromatin within the flagella cast off by Laveran's parasite. This was indeed a step forward, but it is doubtful whether it became widely known to other workers.

At this point Patrick Manson (Fig 1) entered the arena and took a prominent part in subsequent events. When at the end of 1889 he returned to Scotland from Hong Kong he was still in ignorance of Laveran's discovery nine years earlier. Directly he set up in practice in London in the following year he began to search for the parasite in his Indian seamen patients. Soon he was shown the plasmodia of malaria by Dr H G Plimmer (1856–1918), Professor of Protozoology in the University of London, who had just received his specimens from Professor B Grassi in Rome. Later he showed his own specimens to Ronald Ross when he called upon him in April 1894, and a few days later this was repeated at Charing Cross Hospital (*Lancet* 1894 i, 6). Manson had already made his reputation by proving that a mosquito (*Culex fatigans*) acted as a nurse for the embryo of *Filaria bancrofti*, then known as *Filaria sanguinis hominis*, which developed in the thoracic muscles of this insect being there converted into a larva capable of once more invading man (1878). He found, moreover, that the filarial embryo inside the mosquito's stomach cast its sheath and swam around freely in the blood

[1]It must be remembered that Virchow, with his very great authority, had just described his *Micrococcus malariæ* and in 1879 Professor Klebs and Tommasi Crudeli had made great claims for a rod-like organism – the *Bacillus malariæ* – which they isolated from the air, urine and mud of marshes and the future great malariologist, Ettore Marchiafava, had even championed it.

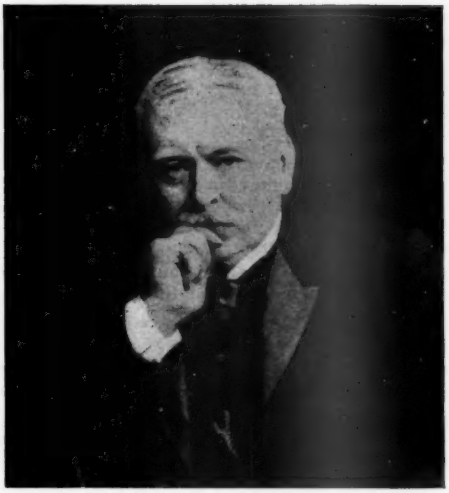


Fig 1 *Portrait of Manson in 1898*

serum. He thought that the larval forms escaped from the body of the dead mosquito into water whence they were imbibed by man. He did not at that time envisage the injection of the parasite into a new host by the mosquito in the *act of biting*. This was not discovered until 1900 by G C Low and S P James. Manson, having discovered in his patients the crescentic form of the subtertian parasite (Fig 2), now began to experiment and to compare the exflagellation that he observed to take place, not in the blood, but only when it had been cooled and withdrawn from the body. It was found that by adding a little water or by breathing on the preparation this process was accelerated. Working in his primitive laboratory at 21 Queen Anne Street, night after night, and refusing to go to bed, he devised ingenious chambers made of wet blotting paper and plasticine wherein he placed drops of blood on coverslips and by fixing the films by heat, when he had watched the process of exflagellation, he was able to obtain permanent stained specimens. It was by this intensive study that he was able to discern the individual flagella (Fig 3), as they broke away one by one, evidently, as he surmised it, on their way to a new host. He envisaged that the flagellum was normally set free within the stomach of the mosquito, then pierced the wall of this organ and developed in some manner analogous to that of the filaria. This then was the gist of Manson's epoch-making mosquito-malaria hypothesis which was published in 1894 (*Brit. med. J.* ii, 1306). It was not till three years later that MacCallum was to prove the true function of the flagellum.

When Ronald Ross called on April 9, 1894, Manson was unfortunately not at home. Manson therefore wrote asking him to call on him at the first possible moment as he was certain from what he (Ross) had already written from India that he had never seen the parasite of Laveran and that he (Manson) would be pleased to demonstrate it to him and he was sure that he then would be convinced.

Transmission

This was in fact what did happen and Ross became a frequent visitor at 21 Queen Anne Street. He accompanied his teacher to his hospitals at the Dreadnought, Greenwich, and at the Albert

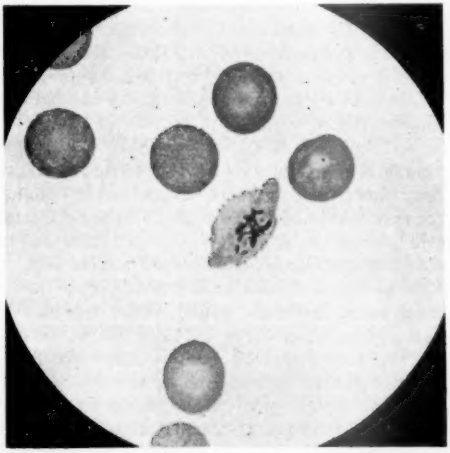


Fig 2 *Manson's preparation of blood with crescent 1894 (London)*

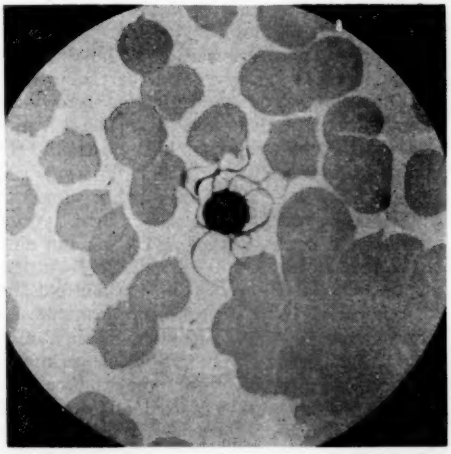


Fig 3 *Manson's preparation of malaria blood made in London in 1894 showing exflagellation*

Dock, and it is recorded that when walking down Oxford Street, Manson placed his hand on Ross's shoulder and exclaimed 'Do you know, Ross, I have formed the theory that mosquitoes carry malaria, just as they carry my filaria'. Manson then approached the India Office through the Secretary, Sir Charles Crosthwaite, as follows:

'I have no hesitation in saying that at the present moment Ross is the best man to carry on malaria investigation. It would be a vast pity if the chance which now presents of making a substantial addition to the pathological science should once more be lost to Englishmen. We are cutting a sorry figure alongside other nations at present. To our national shame, be it said, that few, very few, of the wonderful advances in the science of the healing art which have signalized recent years have been made by our countrymen. But, even in tropical diseases, Frenchmen, Italians, Germans and Americans, and even Japanese, are shooting ahead of us. We have to get a Koch to find for us the cholera germ, and a Haffkine to protect us from it, a Laveran to teach us what malaria is like, a Kitasato to show us the germ of plague, and a Yersin, or a Haffkine to cure us of its effects. But in this matter of malaria, here is a chance for one Englishman to rehabilitate our national character and to point out to the rest of the world how to deal with the most important disease in the world – malaria'.

Ross reached Bombay on April 21, 1895, and immediately started on his great work. He had to find cases infected with *Plasmodium falciparum* and to breed mosquitoes from larvæ, but most important of all he had to persuade his mosquitoes to bite his patients. From April 1895–February 1899 he wrote 110 letters to Manson and received some 85 in reply. In these letters, as well as in Ross's 'Memoirs' (London, 1923), Manson became acquainted with all the stupendous difficulties which Ross had to face. 'Following the flagellum' was like looking for the most microscopic pin in the most macroscopic haystack. He started work seriously at Secunderabad. Every day brought its ups and downs. Everything seemed to conspire to defeat him. The field was vast and the clues nebulous in the extreme. His knowledge of mosquitoes and their anatomy was almost nil and he had no book on the subject to guide him. He was forced to classify them as grey, brindled and dapple-winged and it was not until he returned to London in 1899 that E E Austen, the dipterologist at the British Museum told him what they were. In his dissection of mosquitoes he found almost every parasite – nematodes, coccidia, gregarines and fungi – which are known to infect these insects from time to time. His malaria patients were wayward and unreliable and were sometimes intimidated by scares of plague and cholera and of the Yersin and Haffkine inoculations which were used against them. The things he found inside his mosquitoes might well have represented developmental stages of the malaria parasite and then there were those brown pigmented Ross's spores so frequently encountered, and no one even now knows what they do represent. During all this Manson writes

'Look upon your work as a Holy Grail and yourself as Sir Galahad and never give up the search, for, be assured, you are on the right track. The malaria germ does not go into the mosquito for fun or for the confusion of the pathologist. It has no notion of a practical joke! It is there for a purpose and that purpose, depend upon it, is in its own interest. Germs are selfish brutes.'

Time and time again Ross noted exflagellation of the malaria parasite in the stomach of his mosquitoes but when he tried to follow the flagellum when freed from the parent body, it just dashed away into the tissue and escaped from view.

In October 1896 he concluded that the mosquitoes with which he had so far experimented might not be of the right species, and Manson had even suggested in his Goulstonian lectures (1896) that each species of malaria parasite might require a different one to serve its purpose.

Ross, now 40, was getting weary and disheartened but the predestined day was approaching and the Angel of Fate placed his hand on his shoulder. The dapple-winged mosquito is found. These insects bit at night, had spotted wings and sat on the wall with the tail sloping away from it. The boat-shaped eggs were laid singly; the larvæ had no breathing tube, but floated flat on the surface of the water like sticks.

Success

Ross was in his office at Begumpett: the heat was oppressive and his brow covered with sweat: the screws of his microscope were rusted with damp from his forehead and hands, while his last remaining eye-piece was cracked. The dapple-winged mosquitoes had been found (*Anopheles stephensi*) and he had fed them on his patient, Husein Khan, who had crescents in his blood. It was on August 20, 1897, which was a dull, cloudy and hot day. At 1 p.m., so he relates, he determined to sacrifice the seventh of the batch of mosquitoes fed on August 15, and when dissected and placed under the microscope, there in the stomach empty and placid before him lay a courtyard of flagstones (or cells), each one of which must be scrutinized – a task which would take half an hour at least. He was tired and disheartened. But fortunately he saw an almost perfectly circular outline before him of 12μ in diameter. The outline was much too sharp and the cells too small to be an ordinary stomach cell of a mosquito. He looked still further and here was another and another exactly similar. In each of them was a cluster of small granules, *black as jet*, exactly like

the pigment of the *Plasmodium* crescents, and as with that the granules numbered about twelve to sixteen in each cell. How then did the pigment get into the cell? Could it have been absorbed from the ingested blood in the stomach? Then Ross remembered what Manson had said, namely that, whatever the form the developing parasite assumed, it would certainly contain malarial pigment. The next day he slew and dissected the last surviving mosquito and there were the cells again, twenty-one of them just as before ,but this time *much larger*. The thing was done. Εὑρηκα! The greatest advance in malariology had been made since Laveran's discovery of the parasite and Ross had in a trice become an immortal.

The preparations, mounted in formalin and glycerin, were despatched by mail to Manson in London. They were examined by him on September 13, 1897: drawings were made of eleven oöcysts and appeared in the *British Medical Journal* in December 1897 (ii, 1786). Manson had cabled back to Ross 'Congratulations, you are on the right road at last'.

And now there chanced a fortuitous and most important find which went far to fit the parts of the jigsaw together and smooth the path for the discovery of the life history of the malaria parasite. The function of the *flagellum* was fully explained by W G MacCallum, then a young student, who subsequently became a famous pathologist. During the summer of 1897 and while on holiday at Dunsville, Ontario, he studied the *Halteridium* of the crow and found that the flagellated form of this parasite was the male and the spherical form the female element. He furthermore showed that, after fertilization, the latter became converted into a 'travelling vermicule' which was highly motile and entered stomach cells. On his return to Baltimore he repeated his observations on the crescents of subtertian malaria. The thread-like flagella were, indeed, microgametes and functioned like spermatozoa. This information was passed as quickly as possible by Manson to Ross and is explained in a letter dated February 7, 1898. 'In the derivation of pigment in the oöcyst [using this term for the first time] you should go over MacCallum's observations on halteridium' and later, on April 29, 1898 'You have to thank the plasmodium that it is fool enough to carry its pigment dung along with it into the mosquito's tissues. Otherwise, I suppose, you would have never spotted him.'

Very shortly after his momentous discovery Ross had a second piece of good fortune and was enabled to reinforce his findings by feeding a number of small and more delicate mosquitoes with brownish-white dapple-wings (*Anopheles culicifacies*) on a case of benign tertian malaria. Some forty-eight hours subsequently he found a number of similar pigmented cells, of smaller size, in the stomach wall.

Just as Ross had at last made a noticeable advance and victory loomed in sight, he was ordered away on military duties to Bombay and with this ended his work on human malaria. As it so happened further attempts were useless on account of the disturbance and riots caused by Haffkine's inoculations against plague and cholera. However, in March 1898 he was given the use of D D Cunningham's laboratory in Calcutta and decided to continue his research with proteosoma of birds. Manson had already urged him to do so and now he had relented. 'What an ass I have been', writes Ross 'not to follow your advice before to work with birds. The technique is much easier'. Soon this encouraging statement reached Manson:

'My one wish is that you were here to share with me the pleasure which I have experienced yesterday and to-day in seeing your induction being vertified, step by step. Such pleasure comes to but few men, I fancy, though you must have felt it with regard to filaria.'

Again, on April 5, 1898:

'I am producing pigmented cells *ad libitum* by feeding grey mosquitoes (*Culex fatigans*) on larks and sparrows infected with proteosoma. This, of course, means the solution of the malaria problem. What a beautiful discovery this is! I can venture to praise it because it belongs to you, not to me. I sometimes think that it is the prettiest thing in the whole range of pathology.'

In Mahomed Bux, his faithful laboratory attendant, Ross had found a natural genius who instinctively knew all about the habits and rearing of birds and mosquitoes and how to find them.

Ross's report to the Director-General is entitled 'Cultivation of Proteosoma, Labbé, in grey mosquitoes', was dated May 21, 1898, but published in November 1898 (Fig 5), and in its conclusion he stated

'These observations prove the mosquito theory of malaria as expounded by Dr Patrick Manson, and in conclusion I should add that I have constantly received the benefit of his advice during the enquiry. His brilliant induction so accurately indicated the true line of research that it has been my part merely to follow its direction.'

By June 1898 he was able to demonstrate germinal threads (sporozoites) inside the coccidia (oöcysts) and to depict with accuracy the germinal rods pouring out of the disrupted mature cyst (Fig 4). Later in July 1898 he announced the discovery of the salivary glands of the mosquito packed full of these rods. The next step was the infection of healthy sparrows by the bite of infected mosquitoes. This was also soon successfully accomplished and the epoch-making story was announced at the meeting of the new Tropical

like granular material I am not sure whether they are at all motile, though I have often thought so: I think especially that they are bent & straighten themselves: but these points are very difficult to ascertain because of their continual brownian movement: while it is evident that both water & salt solution kills them

When mingled stained Coccidia are burst their bodies seem attacked like rays to encircle cells

Calcutta
28th June 1898

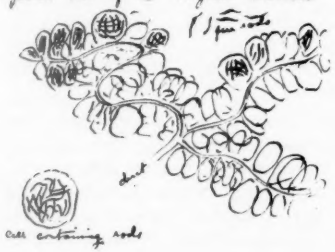
Dear D. Manson,

I despatched three copies of my report to you by this mail vid one for Sir J. Fayrer. You will oblige me greatly by sending it on to him. I don't know his address but will write to him as well.

I fear much I shall be able to send you good second-day specimens as my infected birds are so much better that they don't yield good crops any longer, but will try tomorrow.

The third of the copies of my report are not — I fear — you will ever get and will never

pouring out from somewhere in streams. Suddenly to my amazement it was seen that many of the cells of this gland contained the germinal rods of proteosoma. Coccidia within them. Looking further the cells of the whole lobe of the gland were simply packed with them, and on bursting the cells the rods poured out of them just as they pour out of the ripened coccidia



The rods were quite unmistakable, having the tapering, flattened & vacuolated structure peculiar to them. They are identified at once & no structure like them exist in the normal mosquito. Then they were in the cells of the gland. The cells were not coccidia. They are only 25 μ in diameter, have a very thin outline & contain a perfectly clear fluid, without granulations or oil-drops such as the Coccidia possess. The rods lay within them quite regularly & motionless except for brownian movement. In one lobe almost every cell contained numbers of rods; in other lobes only one or two cells contained them. By the attachment of the cells to the

Fig 4 *Letter from Ross to Manson June 25, 1898 describing the life-cycle of the malaria parasite*

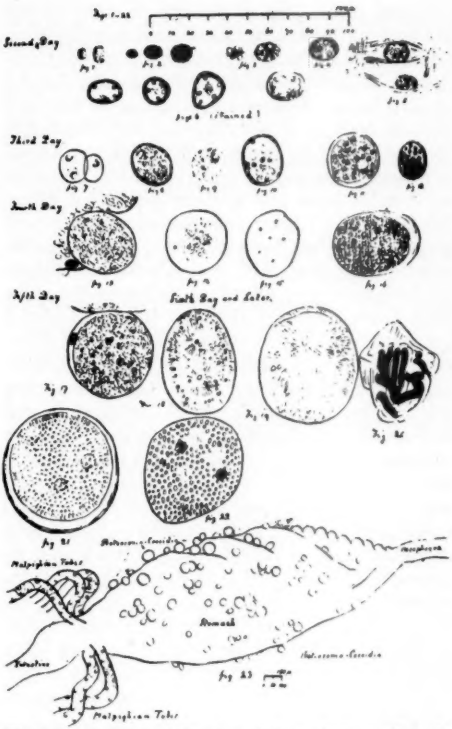


Fig 5 *Ross's original drawing of the malaria cycle in the mosquito. Secunderabad, India, published November 1898*

Diseases Section of the British Medical Association in Edinburgh on July 26–29, 1898.

Ross left India for good with the great problem solved on February 16, 1899. Before his departure Dr C W Daniels, who had been sent out by the Royal Society to verify Ross's results, arrived on December 22, 1898. It was not long before he was convinced that Ross was perfectly right and soon he with a Dr Rivenburg succeeded in infecting 12 out of 22 healthy sparrows by the bites of *Culex fatigans* so that Daniels was able to send his confirmatory report to the Royal Society on January 28, 1899. In the year 1899, and again in 1901, Ross was able to verify the correctness of his proteosoma work in regard to human malaria in Sierra Leone and the Gambia.

The Advent of the Italian Contingent

Towards the end of 1898 at a time when Ross was convinced that the solution of the malaria puzzle was right at hand he became aware that he might expect contradiction of his claims from Battista Grassi in Rome. On October 8, 1898, Manson told Ross that he was sending Grassi one of his specimens to Rome and two to Dr J Edmonston Charles, a retired Deputy Director-General of the Indian Medical Service, who was living there. It has never been clear what part Charles played in this critical malaria problem. He no doubt acted from the best motives, but he functioned as a kind of secret agent for both sides in so far as he acquainted Manson, and Ross, with all the titbits of information he could ferret out from the Grassi-Bastianelli combine and in return he furnished them with an up-to-date account of Ross's researches in India which Manson served up to him. It is quite clear now that Grassi could not make any further progress until he had got full details of Ross's epoch-making discovery of August 20, 1897. Ross writes

'After this Drs A Bignami, G Bastianelli and Professor B Grassi of that city gradually carried out for Italy the local researches which I had always considered would constitute the second part of my investigation.'

This move tallied with a communication from Patrick Manson under the date of November 8, 1898:

'I fear that these "furriners" are inclined to filch as much as they can. This is a sentiment I only breathe to you. We will take care that your interests are looked after here.'

Ross's comments on news from Rome are as follows:

'The Roman writers possessed many advantages over me. They were free to do as they pleased, they could publish their results a few days after obtaining them; there were numerous well-known intensely malarious spots close at hand, and there were many hospitals, laboratories and professors to consult, if necessary. Lastly they had good libraries and all my experience and writings to guide them.'

Finally on leaving India and as the ship sails down the Hooghly he writes

'Well, I have left many things undone which I ought to have done, but congratulate myself that the task you imposed on me is finished. You must certainly cease *rubbing the lamp* for a little, at all events' (February 24, 1899).

Now Giovanni Battista Grassi (1854–1925) occupied the stage and to him belongs the credit and the whole credit of transmitting human malaria (*Plasmodium vivax*) from one man to another via the mosquito *Anopheles claviger* (*vel. maculipennis*) (Fig 6). Grassi was not a doctor, but he was a great zoologist and his record in pure

Fig 6 *Grassi's drawing of* Anopheles claviger (maculipennis) *in Rome, July 1898*

zoological research was such that it constituted an achievement almost unparalleled in the whole history of zoology. Just to mention a few of the items: he had worked out the life-history of the common eel (*Anguilla anguilla*) and had proved that what was considered a new marine animal (*Leptocephalus brevirostris*) was really the marine larval stage of this creature. His work published in 1913 is still a classic account of the genus murenoides. He had rendered great service to helminthology and also to entomology in the life-history of the sandfly phlebotomus, to agriculture he furnished a similar boon by his work on phylloxera, a parasite of the vine, but his finest work had been on the constitution and development of the society of termites for which he was awarded the Darwin Medal of the Royal Society in 1917.

His malaria work really commenced on July 15, 1898, when he toured Italy, especially the malarious villages in the vicinity of Rome and the Roman Campagna. He was much better equipped than Ross had been in his knowledge of entomology and he worked out the distribution of mosquitoes in relation to the incidence of malaria. He estimated that he had to deal with between 30 and 40 species, but he was soon able to eliminate some 24 from his list when he found that they had bitten children without producing malaria, but then he found one whole family down with fever; the father averred that there were no mosquitoes, but Grassi, down on his hands and knees, found them hidden behind the furniture and pictures on the wall. He described these mosquitoes as being quite unmistakable. Attracted by light they had gay wings with four dark spots and when at rest stuck out their abdomens in a most shameful manner and he noted that this species (*Anopheles maculipennis*) in some places preferred the blood of horses to that of man. He employed small boys to catch them and when he had collected sufficient he loosed them in his room where he lay naked on his bed, but they consistently refused to suck his blood; instead they swarmed in next door and bit his mother, fortunately without any ill-effects.

However, in November 1898 Grassi had better fortune. Signor Sola was a patient in the Santo Spirito Hospital in Rome. This stands on an eminence and the room in which the patient lay overlooking the Vatican City was 600 feet above the level of the sea. No mosquito had ever been seen in this room which the patient had occupied for *six* years under the care of Dr Guiseppe Bastianelli. After several failures with wild-caught mosquitoes Grassi hastened to his favourite village, Moletta, where everyone was stricken with malaria and brought back some with spots on their wings and let them loose in Sola's room. Ten days later Sola was down with a typical malarial rigor and eventually benign tertian malaria parasites were found in his blood. Grassi had courted success and had for the first time undoubtedly completed the human cycle in the malaria story. However, in so doing he had laid himself open to attack, because the experiment took place in Rome itself, a city which was known as an endemic centre of malaria. He was criticized by Ronald Ross and eventually branded as an 'Italian robber'. Later by means of dissection and paraffin sections he was able, together with Bignami and Bastianelli, to trace the whole story of the human parasite which followed the same lines as had been described by Ronald Ross for the proteosoma (*Plasmodium relictum*) of birds. On November 28, 1898, they reported their findings to the *Academie dei Lincei*. Grassi described the complete life-cycle of *P. falciparum* and Bastianelli and Bignami did the same for the quartan *P. malariæ* and, later, the team showed that two other species of anopheles, *A. superpictus* and *A. bifurcatus*, were capable of transmitting malaria parasites. Finally in 1901, Grassi, with the association of Ettore Marchiafava, produced a beautifully illustrated monograph (Die Malaria. Studien eines Zoologen. 2nd ed. Jena) of the life-histories of the three different species of plasmodia in the body of anopheles – all made from original specimens and which placed the work of these Italians on a plane only second to that of Ronald Ross.

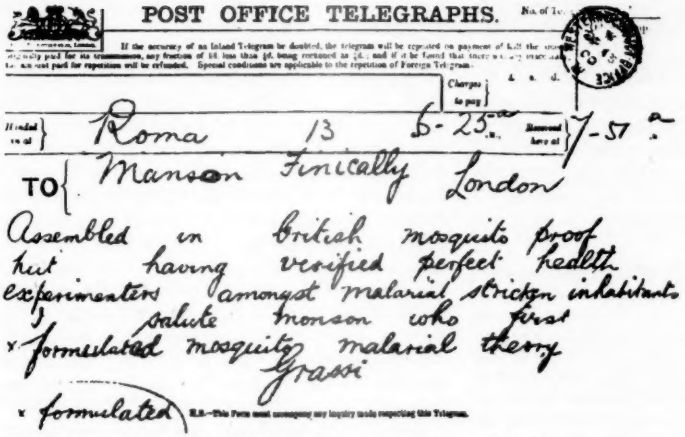
The attitude of Grassi towards Patrick Manson and his work has always appeared impeccable, especially when, in September 1900, he visited Ostia in the Campagna to inspect the work of Manson's team in his famous mosquito hut and sent the telegram shown in Fig 7.

Now we can switch back to Manson who, in the meantime, had not been idle. The practical outcome of Ross's work in India had been left in his hands since they felt that the Colonial Office and the British public were still sceptical about the idea of mosquito transmission of malaria.

Sequel

It is difficult at the present day to realize the feelings of the man in the street at that time. Manson's name had been widely publicized as 'mosquito Manson'. The comic papers depicted dense clouds of mosquitoes issuing from beer barrels and falling upon the innocent public, while the Legislative Council of Barbadoes issued a resolution that it was against the will of God and that the idea that mosquitoes carried malaria was entirely false as it was not printed in the Bible.

The first experiment was conducted by Dr G C Low with Dr L W Sambon, the artist Signor Terzi, with an Italian servant, Silvestri. They lived in a wooden mosquito-proof hut, constructed by


POST OFFICE TELEGRAPHS.

Roma 13 6-23 7-57

TO Manson Finically London

Assembled in British mosquito proof hut having verified perfect health experimenters amongst malarial stricken inhabitants I salute Manson who first formulated mosquito malarial theory Grassi

formulated

Fig 7 *Telegram from Grassi in Italy (Rome) September 7, 1898*

Humphreys in England and erected at Fumaroli in the Roman Campagna, near Ostia. The windows and doors were protected by wire gauze and the beds were covered with mosquito nets. In the daytime the experimenters roamed about the countryside amongst the malaria-stricken inhabitants, but every night before sunset to one hour after sunrise they remained shut up in their hut. From early July to October 19, 1900, they remained in good health and took no quinine. In this humble situation they were visited by many scientific workers from Rome, including King Umberto of Italy. At the same time and very judiciously, the opportunity was taken to put the experiment into reverse, so to speak. *Anopheles* (*A. maculipennis atroparvus*) were fed in the same Santo Spirito Hospital on malaria cases (*P. vivax*) by Bignami and Bastianelli. They were then contained in specially constructed gauze cages devised by Sambon and enclosed in a specially designed box. They were then despatched from Brindisi by the agency of a special messenger in the Embassy bag to London. In all there were three consignments of live mosquitoes containing malarial oöcysts. These gauze cages were removed from the box and applied to the back of the hand and were set to bite Patrick Thurburn Manson, the eldest son of Patrick Manson, a student at Guy's Hospital, aged 23. The first experiment failed, but the other two succeeded. He developed benign tertian malaria fifteen days later, and eventually malaria parasites (*P. vivax*) were found in his blood. He suffered subsequently from two relapses in the following year.

There could be no answer to these planned experiments which were conclusive, and so with this the consecutive and essential narrative of the malaria story comes to its end.

Dissension

There were, however, intruders into this malaria story and the chief of these was Robert Koch of Berlin. Unfortunately, owing to his many victories in other spheres he had acquired a 'halo' and had become the hero of the German public. No sooner had he heard through the medical press of Ross's progress in India, than he began to interest himself more actively in the malaria story. He had learned in Tanganyika where he had been for one and a half years that the natives of the Usumbura mountains used the same name for malaria (*Mbu*) as they did for mosquitoes. On his return to Berlin in May 1898 he received a popular ovation. On June 15, at Imperial command, he delivered an oration in the Assembly Room of the Kaiserhof Hotel in Berlin under the German flag and with the band playing German tunes. The room was packed with high military officers, the General Staff and many officials. It is recorded that the only tropical aspect of it was the unbearable congestion and temperature. Not a word was uttered about Manson or Ross and he suggested that probably mosquitoes laid eggs in the human body and that then the malaria parasites issued from them and entered the blood stream, thus causing malaria. He then launched out on a research on his own and accompanied by three professors he arrived at Grosetto, a small town some 10 miles from Rome, on April 25, 1899, and began a research programme which lasted until August 1. He did not have any success with human malaria, but worked with proteosoma (*P. relictum*) in sparrows during which he confirmed Ross's work, but his most original contribution was on the morphology and behaviour of the travelling vermicule. Koch believed in advertising in the popular press and consequently

the newspapers proclaimed that it had been left to a German – Koch – to settle the malaria problem once and for all!

Nuttall in Cambridge writing to Ross in Calcutta on August 13, 1898, says: 'Koch who came back from E. Africa declares himself in favour of the theory and suggests that it would be important to follow up the matter experimentally in mosquitoes. He ignores your work completely'.

Now read the following outburst by Koch on February 10, 1901, to Ross.

'In my opinion, it is not permissible to take account of the moral defects of a man, even if he is a rogue, in considering his scientific deserts so far as he possesses any. For this reason, although I consider Grassi to be a rogue and a robber in scientific domains, I should not pass over his scientific deserts where they ought to be mentioned, but it is my conviction that he has no such merits. What he claims as his is either stolen or fabricated and the remainder is too small for me to consider myself under any obligation to mention as a valuable addition to knowledge, for instance his statement regarding the development of the malaria parasites in the stomach of the mosquito, if he really saw them, as he states (which, by the way, I do not believe).'

Unfortunately, Grassi is not the only one in Rome to manufacture science in this manner. But Nuttall has this to say in 1924, 'When Metchnikoff brought malaria blood films from Russia in 1889 and demonstrated them to Koch he was treated with scant courtesy, because Koch still disbelieved in the existence of the malaria parasites that Laveran had discovered in 1880. Koch denied that Metchnikoff's slides showed malaria parasites, though the latter had demonstrated the excellent preparations to Professor Flügge and myself some days previously in Breslau. In the case of Grassi, Bignami and Bastianelli in Rome the antagonistic attitude of Koch was extreme. It was generally held in Berlin that the work of the Italian observers was worthless'.

All this work, so wonderful in itself, aroused jealousies and virulent abuse in the various participants. The vultures and the jackals quarrelled over the carcass and of all Manson alone remained serene and composed. 'What I have done, I have done,' said he, 'I never reply or retaliate'.

Ross has this to say about Grassi in *The Times*, February 5, 1908:

'Sir, After a man has spent years over the solution of a difficult problem, it is always gratifying to find credit given, not to him, but to those who have performed the easy task of repeating and confirming his work.

'Your correspondent makes out that I performed only the humble feat of cultivating the parasites of birds in mosquitoes, that I failed in cultivating the human parasites and that the Italians did all the important parts of the work. . . .'

Grassi on his part was savage and mendacious. He enumerates (*Lancet* 1901 i, 141) and (*Policlinico* 1900, **7-M.,** 593) the results obtained by Ross in his experiments with human malaria 1896–1898 and stigmatized them as erroneous, inconclusive, dubious, or positively misleading. Major Ross's discoveries he discounts and claims to have made them himself with Feletti in 1890 on the evolution of proteosoma in the grey mosquito independently of Ross. (This, of course was not true.) Finally he claimed emphatically that the mode of transmission of malaria had been completed for Italy as the result of researches begun by himself and continued with the assistance of Bignami and Bastianelli; *but the credit for the final completion belonged to himself* (Grassi) *alone*!

Some of the statements put forward by Grassi border on the ridiculous.

The extent to which these arguments reached may be judged by the following statements by Grassi in *Policlinico* 1900.

'He (Ross) says that from his experiments came evidence that the mosquitoes with spotted wings were *Anopheles*. No dear Mr Ross, the great word – *Anopheles* – which signified a new era in the study of human malaria, was first pronounced by me.

'We must say from the zoological point of view that the description and many drawings of Ross were so badly done that they cannot be trusted.

'I remain your humble servant, Mr Ross, in continuing this useless polemic, which amuses me,

Prof B Grassi, Rome, November 1900.'

Here Ross intervenes 'More meretricious stuff can scarcely be imagined. Grassi discovered nothing in connexion with malaria'.

And this is what Ross had to say about his former teacher and friend – Patrick Manson:

'Manson was scarcely a very expert investigator partly because he had a shaky hand which further impeded his work, and his later ideas, particularly, proved to be often unsound, especially when they became typically medical.'

(Later in 1930)

'The work was done by me alone, with Manson's occasional advice, it is true, but *not* by his instructions, as frequently pretended. It is, of course, the common duty of all medical men to help each other when necessary, and when I received the Nobel Prize in 1902 I did not feel called upon to divide it with Manson, even if I had thought proper to do so at all.'

Unfortunately towards the end of Manson's life the attitude of Ross towards him progressively deteriorated.

Section of Ophthalmology with Section of Dermatology

Chairman Sir Benjamin Rycroft OBE FRCS
(President of the Section of Ophthalmology)

Meeting November 10 1960

Discussion on Behçet's Disease

Dr G B Dowling (*London*)

Behçet's Disease

Many papers on Behçet's disease published during the past twenty years, open with the statement that the disease was discovered by Behçet and first described by him in 1937. A considerable ophthalmological literature on the subject, however, dates almost from the beginning of the century. For about twenty-five years this was mostly German, though a case was described in French general medical literature by Chauffard *et al.* (1923) with no ocular manifestations but otherwise with almost the whole gamut of the pathology of the disease including encephalitis. These authors regarded the disease as an entity and they believed a filtrable virus might be the cause but could not prove this by the means then available. About that time Fuchs (1926) reported a patient from Istanbul who had recurrent ulceration of the mouth and scrotum, recurrent iritis with hypopyon and an unidentified erythematous eruption. Fuchs thought the picture exotic and possibly related to the patient's environment, and so communicated with his colleagues in Istanbul who, however, were unable to match the case. The next landmarks came from the two Greek ophthalmologists, Adamantiades and Dascalopoulos. Adamantiades (1931) described relapsing oral and genital ulcers, hypopyon iritis, phlebitis, and hydrarthrosis of the knees and observed that attacks of joint, skin and eye symptoms were related to each other in time. He identified his patient's disease with that named 'ophthalmia lenta' by the German author Gilbert (1920). Dascalopoulos (1932) described a case with frequently relapsing uveitis with hypopyon and oral and genital ulcers, remarking that the presence of aphthosis in this type of uveitis was so constant that he proposed to call it 'relapsing aphthous uveitis'. Each ophthalmologist who encountered this rare disease and wrote about it never failed to refer to the work of his predecessors. No doubt the seriousness of the ocular disease, leading usually in the long run to blindness or near blindness, at least in one eye, demanded the closest possible study of all available information.

The most productive phase in the ophthalmological literature seems to have ended here. Besides the outstanding contribution of Chauffard *et al.*, it had been accompanied by much non-ophthalmological literature which stemmed from early observations by Neumann (1894) on a number of cases of oral and vulval ulceration, some associated with erythema nodosum or erythema multiforme. This story is well known to dermatologists as are the various names which the condition acquired, such as Neumann's aphthosis, ulcus vulvæ acutum (Lipschutz), periadenitis necrotica mucosæ oris (Sutton) and others. Thus two parallel series of clinical observations, ophthalmological and dermatological or gynæcological, belonging, as is now obvious, to the same disorder, failed to meet for many years. Adamantiades & Lorando (1949) perhaps found the clue, drawing attention to the fact that all the dermatological descriptions of the 'partial syndrome', that is without ocular symptoms, concerned women with vulval ulceration. Therefore seemingly women with the disease develop the ocular manifestations far less often than men.

The first description by a dermatologist of the wider syndrome was given by Whitwell in 1934. He evidently knew nothing about the ophthalmological literature but he gave a good account of the clinical picture based on 3 cases in which he described recurrent oral and genital ulcers, relapsing iritis in one case, erythema nodosum, a recurrent papulo-pustular eruption and deep thrombosis in a leg. He noted that the attacks of iritis were preceded by relapses of ulcers and the papulo-pustular eruption by a day or two.

Finally in 1937, Behçet described the same clinical picture, also on the basis of 3 cases, and put forward two ætiological hypotheses, first a viral hypothesis based on finding in abundance what he thought were inclusion bodies in scrapings from the ulcers, and second that of a distal

response to focal infection. The inclusion bodies have not since been seen by anyone and the observation must presumably be regarded as erroneous. He too seemed to know nothing of the ophthalmological literature or even of Whitwell's description three years earlier, for he acknowledged no previous account of the disease in its wide aspect, referring in discussion only to Lipschutz's ulcus vulvæ acutum and to some unrelated disorders such as esthiomene, dermatitis herpetiformis and the Stevens-Johnson syndrome.

Within a few years the syndrome was to become known universally as Behçet's syndrome or disease and after 1949 almost nothing further is heard of Lipschutz's ulcus vulvæ.

This term has served to provide one name, which everyone knows, for a disease which has had too many and suggests the first question for discussion. How ought Behçet's disease to be defined; can it be defined closely or is it a vague concept? Two extreme views have been expressed and both have received support. The first is that the common oral aphthosis is part of the syndrome, and Touraine (1950, 1955), its principal exponent, divides the disease into aphthosis and major aphthosis (*grand aphthose*), the latter including the so-called Behçet triad and all the other manifestations. At the other extreme is the view that Behçet's syndrome, Stevens-Johnson syndrome, ectodermosis pluriorificialis (these two appear to be the same) and Reiter's disease are all one, named 'muco-cutaneous-oral syndrome' by its supporters (Robinson & McCrumb 1950, Bøe *et al.* 1958, Scott 1958). Supposing both of these extreme views are rejected, what criteria of diagnosis may be accepted?

Analysis of 124 case reports of the wide syndrome from 1906 to 1959 seems to depict a disease with a strong individuality in spite of its wide variety of manifestations (Table I). No case consisting only of oral and genital ulceration is included in this analysis.

Curth (1946) thinks that the combination of oral and genital ulceration ought to be regarded as enough for the diagnosis and I suspect that that opinion will receive much support. Theoretically any two or more of the various manifestations could be enough but the figures show plainly that the greatest diagnostic importance should be attached to the ocular disease and the oral and genital ulceration one or more of which are likely to be included in the picture sooner or later. Perhaps it ought to be emphasized that according to the numerous case reports it is clear that these various manifestations can appear in any order, for example eye manifestations can precede oral or genital ulceration by years, though in most cases the ulcers have appeared first.

Table I

124 cases of Behçet's disease illustrating relative frequency of manifestations

Relapsing oral ulcers	112	(90%)
Relapsing genital ulcers	104	(84%)
Relapsing iritis with hypopyon, choroido-retinitis, &c.	99	(80%)
Other eye symptoms, described as conjunctivitis, kerato-conjunctivitis, episcleritis	6	(5%)
Relapsing hydrarthrosis, arthritis, arthralgia	43	(35%)
Pustular skin lesions	38	(30%)
Erythema nodosum	35	(28%)
Other skin symptoms, erythema multiforme, nodules, purpura	16	(13%)
Thrombophlebitis	15	(12%)
Disease of the central nervous system usually described as meningo-myelo-encephalitis	24	(19%)
Epididymitis	7	(6%)
Diarrhœa	4	(3%)

The next question is whether or not the oral ulcers of Behçet's disease can be distinguished clinically from the common oral aphthosis. Some say that this is impossible but it seems also to be recognized that the deep excavating ulcers which are seen quite often are, or may be, different. Vulval ulcers may be very deep and persistent, occasionally perforating the labia minora. The dermatologists would like to know whether, in the absence of other evidence, ophthalmologists can recognize the relapsing ocular disease as something special and belonging specifically to this syndrome. Early authors described some cases with and some without such additional lesions as erythema multiforme or erytherma nodosum or oral or genital ulcers. A few continue to use the term 'ophthalmia lenta' proposed by Gilbert (1920), one of whose three original cases had ocular symptoms only.

Pathology

It would be convenient and it would help us to understand the disease better if it could be readily distinguished by some basic morbid anatomical feature. Pathologists have had few satisfactory opportunities for studying Behçet's disease because patients rarely die of it in hospital unless the central nervous system is involved. The somewhat frequent occurrence of thrombophlebitis might be thought to point to a basic primary vascular lesion and attention has been drawn to thromboses of retinal vessels (Jebejian & Kalfayan 1946), of small veins in the base of ulcers (France *et al.* 1951), and in the erythema nodosum-like lesions (Jebejian & Kalfayan 1946, Thomas 1947). It has also been remarked that thromboses of small vessels can be seen often in ulcers of whatever origin and that although the tiny necroses of the central nervous disease could conveniently be attributed to infarction, yet no disease of the small vessels of the brain, brain-stem or spinal cord has yet been seen (Pallis & Fudge 1956).

The curious skin sensitivity of Behçet's disease was first observed by Jensen in 1941. He noted

that the tuberculin, Frei and dmelcos skin tests were all positive and, finding that a positive reaction could also be produced by injecting normal saline, considered them non-specific. A needle prick on any part of the skin produced after twenty-four hours a small pustule with surrounding redness and the same happened after pricking the oral mucous membrane. A prick on the scrotum produced a pustule with surrounding redness which was deeper in colour and more infiltrated than the corresponding lesion on other parts of the skin. This scrotal lesion later became crusted and eventually ulcerated and could not be distinguished from the spontaneous scrotal ulcers. Jensen noted that such reactions were maximal at the height of an attack while during a remission the reactions, though positive, were much less pronounced. These observations have been repeatedly confirmed by others. Positive skin reactions provoked by the intradermal injection of autogenous extracts of ulcers (Jadassohn *et al.* 1957) or of regional glands (Bonnet *et al.* 1953) could perhaps also be non-specific.

Ætiology

The disease begins in the majority in the third decade (Table 2). Although about twice as common in males as in females (Table 2), the male preponderance vanishes if one is prepared to accept cases with combined oral and genital ulceration as belonging to the disease, for reports of these, and these are many, concern females almost exclusively. Analysis of the wider syndrome shows that 14 out of 45 females and 5 out of 79 males escaped ocular disease. Altogether the facts appear to indicate that female patients with the disease are more likely to escape the ocular manifestations than males.

Table 2

Age of onset		*Sex incidence*	
0 – 10	0 patients	Males	79
11 – 20	30	Females	45
21 – 30	45		
31 – 40	27	*Ocular symptoms*	
41 – 50	14	Males	74
51 –	3	Females	31

Geographical Distribution

It has often been said that most of the reports of cases are from countries bordering the eastern end of the Mediterranean. If this is so the geographical factor must be of great ætiological significance. However, analysis of published cases, while not necessarily reflecting the real distribution, suggests hardly more than a moderate preponderance in the Middle East compared with the rest of the world (Table 3).

Table 3

124 cases of Behçet's disease showing geographical distribution at time of onset

Eastern Mediterranean area: Greece, Turkey, Armenia, Lebanon, Palestine, Jordan, Egypt, Libya	29 cases
Great Britain	29
Germany	13
Italy	10
Scandinavia including Denmark	9
United States	7
France	7
Holland, Belgium, Algeria	3 each
Switzerland, Russia, Argentine	2 each
Australia, Portugal, Poland, Chile, East Africa	1 each

The principal question concerning the ætiology of Behçet's disease is that which, as far as we know, was first put forward by Chauffard *et al.* in 1923: whether or not it is due to a viral infection and if so whether the causal virus has been isolated. There is a good deal of literature on this, most of it describing repeated failure to isolate a virus from pathological material, even in laboratories fully equipped for virus work (Chauffard *et al.* 1923, Curth 1946, Katzenellenbogen 1946, Jebejian & Kalfayan 1946, Zeavin *et al.* 1956, Jadassohn *et al.* 1957, Garde *et al.* 1958, Duperrat *et al.* 1955).

There have been two principal claims that a virus has been isolated. Sezer in Turkey (1953, 1956) claimed not only to have done this but to have reproduced the disease in mice and rabbits, the latter exhibiting nearly all the manifestations encountered in man. Then Evans *et al.* (1957) grew a virus but could not infect any laboratory animal with it. They based a claim that their agent was probably the cause of the disease on complement-fixation and virus-neutralization tests.

I do not feel that clinicians can be asked to comment critically on this matter.

There remain the questions of prognosis and treatment. The reports do not suggest that complete and permanent recovery is to be expected but this might not be the universal experience. Regarding treatment it would seem that the main effort at present is directed, in severe grades of the disease, towards getting whatever help is possible from corticosteroids. The value of that treatment, in suppressing symptoms, especially ocular symptoms, may perhaps be a suitable point for discussion.

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Virological Aspects of Behçet's Disease [*Abridged*]

The ætiology of Behçet's disease has long been a subject for discussion and debate. Many different causes have been suggested but the principal question before this Meeting is whether or not this disease, or disease complex, is caused by a virus. The evidence in favour of a viral ætiology appears to stem from two sources. First, a general impression that a virus is responsible because no other cause has been found – a view first put forward by Chauffard *et al.* (1923), although they had no evidence with which to support the claim, but it is a view which, nevertheless, has continued to receive support. And secondly, there are a number of reports of virus studies which need careful consideration. Behçet (1938, 1939) was the first to back up the viral concept with evidence of his own personal observations on the microscopical examination of smears made from hypopyon fluid and aphthous ulcers. Fifteen years later Sezer (1953) in Istanbul reported the isolation of a virus from three cases and a few years later made a further report on the properties of this agent (Sezer, 1956). The results of animal experiments in three cases of Behçet's disease were recorded by Alm and Öberg (1945). More recently Evans *et al.* (1957) in this country reported that they had isolated a virus from a fatal case with meningo-encephalitis. In view of these findings can it now be accepted that the viral ætiology of this disease has been established? For a number of reasons the answer still seems uncertain. If Behçet's disease is caused by a virus, and in this context we should include the 'large' viruses of the psittacosis - lymphogranuloma - trachoma group, then this virus must either be a member of one of the recognized groups of viruses, poxviruses, enteroviruses, myxoviruses, arborviruses and so on, in which case one would expect to find some similarity between Behçet's disease and other virus infections; or else the causative agent is a 'new' virus hitherto not recognized but even if this were so one would also expect to find some feature of the disease or property of the virus in common with virus diseases as a whole. The first step, therefore, in trying to answer this question on ætiology, is to compare in general terms Behçet's disease with established virus infection from the point of view of natural history, pathogenesis and pathology.

Natural History

The importance of viruses in human and veterinary medicine can be directly attributed to their role as agents of infectious disease. The way in which viruses are disseminated in nature and the degree of infectivity varies considerably from one disease to another. The acute exanthems and other diseases spread by droplet infection are highly contagious. An animal reservoir may be an essential part of the life cycle of some viruses as, for example, psittacosis; with other virus diseases such as the encephalitis group (arborviruses) vectors play an essential role in transmission; others are spread only by close contact, for example herpes simplex, vaccinia or contagious pustular dermatitis or even closer still in rabies in which virus has to be introduced through a wound for infection to take place. Despite this varied picture contagiousness in some degree or other remains the dominant feature of virus infections, yet it is a feature conspicuous by its absence in Behçet's disease. Epidemics or focal outbreaks are unknown and only rarely has more than one case in a family been reported (Sezer, 1956).

Pathogenesis

Any viral infection such as those already mentioned can be broken down into three essential phases: (1) An incubation period which is symptom free. (2) An infective phase during which virus is present in the tissues, followed by (3) A phase of acquired resistance.

It is now possible with new virological techniques to follow the course of virus invasion in

the animal host in relation to the clinical disease and so build up a picture of the pathogenesis of infection. For example in primary vaccinia the time-relationship between the presence of infective virus and the development of the cutaneous lesion can be followed step by step by the isolation of virus on the chorio-allantoic membranes of chick-embryos. The titre of virus increases until the pustular stage at which the virus content decreases, healing starts and neutralizing antibody appears in the blood-stream. In generalized vaccinia, and in the closely related disease, ectromelia, or mouse-pox, virus is disseminated via the blood-stream and can be demonstrated by similar techniques in the blood, regional lymph glands, certain viscera and in the skin. The third phase, that of acquired immunity is, from many points of view, the most important. The duration of immunity varies from one disease to another. Prolonged immunity is associated with diseases with a long incubation period (e.g. measles and small-pox), blood-stream spread and caused by viruses with a single antigenic strain. In contrast diseases such as influenza or the common cold, characterized by a short incubation period and spread of virus along a mucosal surface, caused by viruses with a number of immunological types and a tendency to undergo antigenic variation, immunity is less durable.

It is difficult to correlate these findings with the symptomatology of Behçet's disease. In particular the recurrent attacks, the length of each attack, the fact that lesions may occur in all three sites together, would seem to put Behçet's disease in a class on its own. Immunity is virtually non-existent in striking contrast to the degree of immunity in viral diseases, in particular those in which blood-stream dissemination occurs. There are exceptions. Trachoma can recur but the pathogenesis is altogether different. Herpes simplex can recur either in the form of a reinfection or recurrent infection in the presence of circulating antibody, but such infections are usually localized and seldom serious.

Pathology

Viruses are intracellular parasites and as such the main effect of virus multiplication can be seen by cellular changes such as necrosis (hyperplasia with tumour viruses) and in some cases by the presence of inclusions. The histological changes in Behçet's disease are mainly non-specific and do not point to a viral infection specific or otherwise. Thus from these three aspects there appears to be insufficient evidence to support the virus theory.

The specific claims for a viral ætiology come next in this process of assessment. It has been stated on numerous occasions in the literature that Behçet (1938) described inclusion bodies in his early cases. In fact Behçet described 'des corps ronds extrêmement petits colorés en rouge-violet, en partie intra et en partie extra-cellulaires'; and later he referred to them as 'les corps élémentaires virutiques'. Unfortunately no indication of the size of these particles is given either in the text or in the photomicrographs, except the statement that 'ces formations rondes étaient environ de la grandeur des corpuscules primitifs de la variole' (Behçet 1938). It would seem therefore that what Behçet was describing were elementary bodies and not inclusions. Without further information interpretation of these findings is not possible.

The most detailed study of Behçet's disease has been carried out by Sezer. In his first report, Sezer (1953) gives details of the isolation of an agent from the vitreous body and subretinal exudates in 3 cases. This agent produced pock-like lesions on the chorio-allantoic membranes of fertile eggs and sometimes death of the embryo. It was transmissible in series in fertile eggs by a number of routes; it produced signs of encephalitis in mice and a disease in rabbits similar to the human disease. Guinea-pigs inoculated by a number of routes developed a fatal hæmorrhagic lobar pneumonia. The agent isolated passed through a Seitz E.K. filter and from electron-microscopic studies the size of the particle was estimated at 100 millimicrons. Antibody could be demonstrated in the serum of 12 patients with Behçet's disease, in 3 experimental animals but not in 15 controls. In a further study on 14 patients Sezer (1956) reported that virus had been isolated from the blood of all 14, the blood cultures being positive for two to three weeks although most of the patients had significant levels of circulating antibody at the time.

Alm and Öberg (1945) were able to transmit an infection to rabbits through four generations. Liquor (presumably spinal fluid) and filtrated sputa were inoculated into rabbits by the intra-ocular and cisternal routes. The summary of this paper in English refers to Behçet's disease as Stevens-Johnson disease. Recently Evans *et al.* (1957) in this country reported that they had also recovered a virus by chorio-allantoic inoculation with material taken from the anterior chamber and brain of a fatal case. This agent produced pock-like lesions on the egg membrane, was maintained for 12 consecutive passages but did not produce evidence of infection in animals (cf. Sezer) or in tissue culture. No cross-relationship could be demonstrated between this agent and herpes simplex or vaccinia viruses. Evans and his colleagues were able to demonstrate neutralizing antibody to this agent in the sera of 11 patients with the disease. No detectable antibody was found in 14 sera collected at random.

Despite the difference already mentioned be-

tween these agents, isolated by Sezer and by Evans *et al.*, it seems justifiable to consider them together. There are a number of unusual features about them. The isolations in Sezer's series were only made from the retinal tissues, vitreous and blood, but not from the mouth or genital lesions. The prolonged stage of viræmia in the presence of antibody is an unusual finding and difficult to explain. In most virus infections viræmia is purely transitory and seldom persists in the presence of antibody. There are exceptions, for example serum hepatitis and infectious anæmia of horses, but these diseases have little relation to Behçet's disease. In vaccinia gangrenosa viræmia is prolonged due to a defect in the immunity mechanism but the infection is progressive and never shows any sign of healing. The serological results suggest that antibody to these agents is present only in the serum of patients with this disease, yet one of the features of virus infections is the amount of subclinical infection that occurs. For example in poliomyelitis and herpes simplex antibody can be demonstrated in a wide section of the population without there being any history of clinical disease. The number of controls trials tested in these two series is admittedly small but the results indicate that antibody was confined to those suffering from this rare disease. Finally, there is no evidence of the histological appearances of the pocks on the chorio-allantoic membranes nor is it stated whether the original inocula on passage materials were bacteriologically sterile.

In summary it would appear that this agent of Behçet's disease does not resemble any virus of one of the recognized groups of viruses. It is possible that it represents a completely new group, in which case it would be desirable to examine this agent in detail and now that we have so many new techniques available in virology this is a much easier task than heretofore. With so many viruses being isolated from the body in both health and disease there is a prime necessity in cases of this nature to prove a causal relationship between agent isolated and disease under investigation. For this purpose a revised version of Koch's postulates amended for the virus area has been defined by Huebner (1957). By adhering to this scheme and making use of virus reference laboratories in many parts of the world it should be possible to establish the identity of these agents and to decide if they are the causal organism of Behçet's disease. Until this is done it would seem wise to consider the viral ætiology as 'not proven'.

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Mr E S Perkins (*London*)

Ophthalmological Aspects

One of the essential features of Behçet's disease is its recurrent nature, and the ocular manifestations are no exception to this rule. Although the buccal and genital ulcerations are usually the initial lesions the patient may not seek medical advice until ocular symptoms develop. The responsibility for making the diagnosis will then rest with the ophthalmologist.

The disease usually begins in the third decade, and for some as yet unexplained reason is more common in men than women – 70% of the cases reported in the literature are males. The patient presents with an acute anterior uveitis in one eye, often associated with a hypopyon. The uveitis settles and then recurs, becoming bilateral within the course of the following months. The recurrences continue every few months until gross ocular damage reduces the eye or eyes to a state of phthisis bulbi. Enucleation may be necessary to alleviate the severe pain which is a common feature of the attacks. The eventual outcome is blindness in one or both eyes although complete loss of vision may be delayed for many years.

Although the dominant clinical picture is that of an anterior uveitis Sezer (1953) considers that the ocular disease actually begins in the retina and optic nerve. The initial retinal lesions usually take the form of a periarteritis or periphlebitis, sometimes with thrombosis of either arteries or veins, and occasionally retinal and vitreous hæmorrhages may occur.

In an excellent review of the literature Mavioğlu (1958) found that retinal lesions were reported in 50% of cases, and when it is remembered that the fundus is frequently obscured by the severity of the anterior uveal reaction it is likely that the retina is involved in a higher proportion of cases.

The optic nerve was affected in 15% of the reported cases and this, combined with the other frequent neurological complications and the involvement of the retina, suggests that the virus (if such is the cause) has neurotropic tendencies.

In view of the poor prognosis it is fortunate that Behçet's disease is not a common cause of uveitis. Only 7 cases have been diagnosed in the first 1,700 cases of uveitis investigated at the Institute of Ophthalmology. These 7 cases do, however, bring out many of the salient features of the disease. All the patients were male and the average age at onset of the condition was 29.

Table 1
Some findings in seven cases of Behçet's disease

Case No.	*Age*	*Duration (years)*	*Visual acuity R.*	*L.*	*Buccal ulcers*	*Genital ulcers*	*Other conditions*	*E.S.R.*
1685	46	9	6/60	H.M.	Yes	Yes	Spondylitis	Raised
1413	22	1	6/36	6/36	Yes	–	–	Raised
921	36	14	6/6	P.L.	Yes	Yes	Skin lesions	Normal
474	24	1	6/9	6/9	Yes	–	Cystitis	Raised
283	40	9	6/60	6/9	Yes	–	Arthritis of ankle	Raised
142	47	4	6/6	C.F.	Yes	–	Osteochondritis of hip. Psoriasis	Normal
132	29	1	6/18	H.M.	Yes	–	–	Raised

In 6 of the patients both eyes were involved with recurrent attacks of a severe anterior uveitis. In 1 patient only the left eye has been affected so far. Hypopyon was associated with the uveitis in 1 patient and 1 patient had a hyphæma at the time of examination. A marked vitreous haze prevented detailed examination of the fundus in some cases, but retinal œdema, sheathing of the vessels and venous engorgement were noted in 2 patients and in 1 other patient an active choroidal lesion was seen. Clearly the posterior segment is usually involved as well as the anterior. In the 2 patients with retinal lesions the optic nerve was also affected, producing a papillitis with subsequent optic atrophy. The vision in one or both eyes was reduced to 6/36 or less in all but 1 patient.

All cases suffered from recurrent ulceration of the mouth and 2 had had genital ulceration. Three out of the 7 cases had some form of joint disease, and it is interesting to note that 1 of these patients also suffered from psoriasis, as such an association with Behçet's disease was recently reported by Masheter (1959). Some of the features of these 7 cases are summarized in Table 1.

The diagnosis depends largely on the recurrent nature of the uveitis and the associated lesions of the mouth, skin, joints, &c. A typical hypopyon iritis is an obvious clue to the diagnosis and the most difficult cases are those which present with retinal lesions and little anterior uveal reaction. Reiter's disease, which is characterized by recurrent anterior uveitis, urethritis and arthritis may cause some difficulty in diagnosis but the absence of retinal lesions, combined with chronic prostatitis and the typical radiological changes in the sacro-iliac joints, should serve to differentiate the two conditions.

The treatment of Behçet's disease has been most disappointing. Steroid therapy has been thought to alleviate the uveitis, but appears to have little influence on the final prognosis. If the viral ætiology is considered proved, steroid therapy would be contra-indicated on general principles until an effective chemotherapeutic agent is available.

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Discussion on Bullous Conditions of the Skin and Conjunctiva

Dr I B Sneddon (*Sheffield*)

Bullæ of the Skin and Conjunctiva

There has been little advance in knowledge of the causes of blistering of the skin and conjunctiva since the original description of ocular pemphigus by Wichmann in 1794 or the first reference in the English language by Cooper in 1858.

From the clinical aspect there has been a gradual separation of entities which, because they have a different prognosis, it is important to recognize. We should pay tribute to Rycroft (1934), Klauder & Cowan (1942) and Lever & Talbott (1942) for having made a semblance of order out of chaos.

One of the greatest stumbling blocks has been that the end-result of several blistering diseases of the conjunctiva is a shrunken scarred state, essential shrinkage of the eye which appears, certainly to the dermatologist, indistinguishable whatever the cause. Whilst the changes in the eyes may be similar the skin eruptions which are associated with them are very different and a knowledge of these may assist the ophthalmologist. There are five diseases which are characterized by blisters on the skin and inflammation of the eye – erythema multiforme, pemphigus, benign mucous membrane pemphigus, epidermolysis bullosa and possibly dermatitis herpetiformis. *Erythema multiforme*, which may involve only the mucosæ and is often called the Stevens-Johnson syndrome, is an acute febrile illness occurring mainly in young people and frequently associated with a virus disease of the upper respiratory tract

or with drug allergy. The usual eye changes are an acute conjunctivitis which, as a result of sepsis, may lead to panophthalmitis, but the great majority recover spontaneously in three to four weeks. The other mucous membranes are always involved and there may be a skin eruption typical of erythema multiforme. Just occasionally, recovery is not complete and a progressive adhesive conjunctivitis persists after the illness is over (Wolff 1949, Klauder 1959). This complication is not common, as I have only seen it once in more than twenty cases of the Stevens-Johnson syndrome and this patient also developed adhesions at the angle of the mouth.

True pemphigus, which includes pemphigus vulgaris and vegetans, is a rare disease which occurs equally in males and females in middle life. Untreated it is fatal. The first sign of disease may be in the eye, but nearly all cases show raw erosions in the mouth with no intact blisters and no scarring and accompanied by considerable pain. The skin lesions are small blisters arising on apparently normal skin but the blisters soon burst, leaving large erosions which bleed easily and are slow to heal. Changes in the eye consist of a conjunctivitis which, and this is a vital point, does not give rise to scarring or adhesions. The patient looks ill and the interval between mucous membrane lesions and the onset of bullæ on the skin is rarely as long as a year. Histological examination of the bullæ will show that the blister is intra-epidermal and associated with degenerative changes in the epidermal cells. The less acute variety of pemphigus, pemphigus foliaceus, very rarely involves the eye or mouth.

Benign mucous membrane pemphigus, or *Pemphigoid* as Lever has called it: This condition, commonly known as ocular pemphigus, has frequently been confused with true pemphigus but as a result of the work of Lever (1951, 1953), who showed that the blister in this condition is subepidermal, and clinical studies such as that of Church and myself (1953), the two conditions can be clearly distinguished, often before eye lesions develop. Ocular pemphigus is not so rare as many people suppose but since any mucous membrane or the skin may be the initial site of the condition patients may present to the dental department, the laryngologist, the gynæcologist or the dermatologist, rather than to the eye department. By working backwards from those cases with eye lesions and examining lesions elsewhere on the body it is now possible to recognize the disease before it attacks the eyes. I must also stress that no case of ocular pemphigus ends as a case of true pemphigus; the conditions are entirely separate.

Benign mucous membrane pemphigus is a disease of the aged. The average age of the series Church and I have collected is 66. It affects females more frequently than males in all the reported series and in our own there were 13 females to 4 males. It is, as its name implies, a benign condition and none of our cases died as a result of it. In 9 patients lesions started on the skin or mucous membrane before the eyes were involved, the longest duration before the eyes became affected being three years, though Klauder (1938) reported a case with sixteen years' interval. In only 1 patient were the eyes the only site; in the majority the mouth was involved as well. Scarring is the prominent feature of all the lesions which differentiates it from pemphigus vulgaris. In the mouth intact blisters are commonly seen in contradistinction to pemphigus vulgaris. There may be difficulties in differentiating the scarring in the mouth from the lacy white lines of lichen planus but constant observation may show an intact blister which, if biopsied, will be in the subepidermal position, the epidermis being stripped off the dermis and no degenerative change in the epidermal cells is present. The mouth lesions are not as painful as they look and large eroded areas on the tongue may persist for weeks with little interference with eating. Two of our patients had erosions of the pharynx and œsophagus and 1 developed a stricture of the larynx because that organ was involved. The vulva and perianal skin were affected in 3 patients and the persistent raw erosions with heaped up white sodden mucosa at the edge appeared unlike any other disease seen in that area. Scarring is also a feature of most of the skin lesions for several patients had chronically pigmented and inflamed plaques which blistered over and over again. These plaques tend to be near the orifices of the body, particularly those involved by the disease. The scalp may be the site of a scarred alopecia with sporadic blistering at the edge and in the centre of the scars. When the scalp alone is affected, diagnosis may be difficult but benign mucous membrane pemphigus must be considered if scars and blisters occur together.

I have purposely said little about the eye changes, but the first sign has usually been a rather bulky swelling of the conjunctiva soon followed by adhesions between the palpebral and bulbar surfaces. I have only once seen a blister in the conjunctiva and was unable to biopsy it. There is frequently an acute invasive stage followed by a period of quiescence and such ups and downs make evaluation of treatment difficult. In many of the very elderly patients whom we have followed for five to twelve years, the disease appears to burn out. Contrary to most of the published reports, only 2 became completely blind and these did so despite local and general steroids, contact lenses, division of adhesions and amnion grafting. One man aged 60 progressed

from the onset of the disease to blindness in five years.

Perhaps I can best illustrate the features of the condition by a case history.

A housewife, now aged 76, was first seen thirteen years ago with pruritus vulvæ. Small bullæ were present in the vulva and groins. Two months later her eyes began to water and scarring was found around the lacrimal ducts. Three years later she attended with bullæ in the mouth and adhesions were found in both eyes. Two years after that vulval erosions were again troublesome and adhesions were present between the labia minora and majora. Two years later still, all the mucosal lesions became inflamed and she developed bullæ on the trunk, axillæ and groins. One particularly large lesion appeared on the right thigh. Skin biopsy at that time showed a subepidermal bulla and because the condition was so severe she was started on corticotrophin and later prednisolone. The skin bullæ cleared leaving a scarred area on the right thigh which has persisted. She remains now on prednisolone 5 mg twice a day. The eye condition is static with reasonable vision but gross adhesions. Her mouth has occasional erosions, but the vulva has healed and the persistent skin lesion on the thigh is a pigmented scarred plaque.

Her response to treatment has been repeated by other patients. The oral, pharyngeal, vulval and skin lesions can be partially or completely suppressed by steroids, but the eye changes do not respond well.

Whilst it is true that rare cases of dystrophic *epidermolysis bullosa* may produce scarring and adhesions in the eye and mouth, the history of liability to blistering after trauma from an early age should serve to differentiate the two conditions. I am aware that some of my dermatological colleagues believe that ocular pemphigus is a variety of epidermolysis bullosa. I cannot accept that a disease of old age which gives rise to so many unique features is the same as a genetic abnormality which usually starts at birth and this is neither the time nor place to discuss this theory. *Dermatitis herpetiformis:* I have never seen chronic and persistent eye changes in the usual adult variety of dermatitis herpetiformis and I believe that many cases described in the literature were probably benign mucous membrane pemphigus showing transient generalized bullæ. However, one does see occasional cases of a subepidermal blistering disease with some features of dermatitis herpetiformis affecting the eye.

While dermatologists are accused, I think rightly, of labelling diseases without any knowledge of their ætiology, I hope I have not thrown out too many labels and that you will agree with me that until such time as we do understand the cause of blistering, there is some point in separating these difficult problems which beset us both.

Acknowledgments: I wish to express my thanks to my colleague Dr R E Church who has helped me greatly in this study and my ophthalmic colleagues, Mr A B Nutt and Mr Wellwood Ferguson who have co-operated most willingly by allowing me to see their cases and teaching me something of ophthalmology.

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Mr Barrie R Jones (*London*)

The Ocular Diagnosis of Benign Mucous Membrane Pemphigoid

Dr. Sneddon has pointed out that whilst the end-result of conjunctival shrinkage is much the same whatever causes it, an examination of the skin and mucosæ will nearly always establish a diagnosis.

I should like to add three points.

(1) I believe that the pattern of benign mucous membrane pemphigoid in the eye is sufficiently distinctive to enable it to be recognized on its ocular signs alone in most cases, although it may require a period of observation to distinguish it from other diseases.

Thus, although erythema multiforme may cause a simple catarrhal or mucopurulent conjunctivitis without cicatrization, accompanied in my experience by a fine punctate or filamentary epithelial keratitis with punctate epithelial erosions (Jones 1960), it may give rise to purulent conjunctivitis or an ulcerative conjunctivitis followed by severe scarring. This is the Stevens-Johnson type and is very liable to be accompanied by staphylococcal infection which may result in loss of the globe. But the ocular disease is an acute attack, usually associated with severe systemic upset. The scarring, which may be gross, is focal and after running its course has remained stationary. Simple catarrhal conjunctivitis may recur with erythema multiforme but I have not seen recurrences of the ulcerative conjunctivitis in this disease.

By contrast benign mucous membrane pemphigoid gives a chronic recurrent ulceration of the conjunctiva, usually of insidious onset, not associated with any acute or severe systemic disease. Each episode of ulceration is relentlessly followed by scarring and shrinkage. Bullæ are rarely seen on the conjunctiva because they rupture so

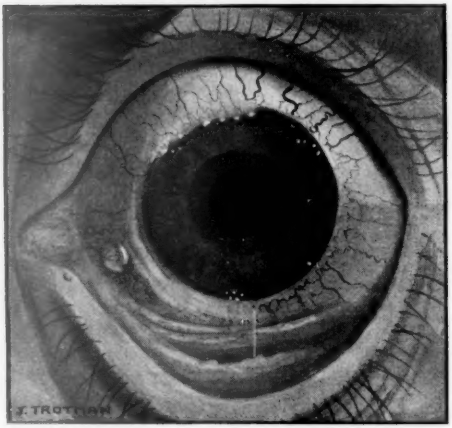

Fig 1 *Early benign mucous membrane pemphigoid showing fresh peripheral punctate corneal lesions, scarring following previous marginal keratitis, a small bulla on the conjunctiva and scarring in the lower fornix following a previous ulceration*

readily (Fig. 1). Punctate epithelial and subepithelial lesions occur, especially in the periphery, and with successive lesions vascular scar tissue invades the cornea which eventually becomes keratinized. Recurrent ulceration is followed by shrinking scar tissue which obliterates the fornices, bridges the angles and results in ankyloblepharon.

(2) All that scars is not ocular pemphigus. The problem lies in the diagnosis of early cases and whilst the ophthalmologist tends to use 'ocular pemphigus' as a label for conjunctival shrinkage, whatever its cause, the dermatologist tends to use the term as a synonym for benign mucous membrane pemphigoid. Each usage is quite justifiable and in order to avoid confusion our case needs an emotionally uncommitted label such as 'conjunctival cicatrization' whilst we look for associated signs in the eye and body generally which would lead to a full diagnosis.

Thus, whilst severe conjunctival cicatrization commonly occurs in trachoma it usually has suggestive signs such as Arlt's line of scarring in the subtarsal groove, pannus and Herbert's pits at the limbus which point to the ætiology even after the follicular and papillary conjunctivitis has burned out. However, the fornix may be obliterated and the differentiation is not always easy.

We have seen cicatricial bands especially at the inner angles in association with rosacea and in one patient very severe but non-progressive cicatrization with loss of fornices followed a staphylococcal granuloma and rosacea (Borrie & Jones 1959).

One of the most confusing things, however, has been the occurrence of cicatrization with keratoconjunctivitis sicca. This can come about in two ways. A scarring conjunctivitis like trachoma, erythema multiforme or benign mucosal pemphigoid may obliterate the lacrimal ductules and lead to a dry eye. On the other hand I have seen sufficient cases of otherwise typical Sjögren's disease to convince me that this condition can give rise to conjunctival shrinkage. It tends to be a diffuse fibrosis, especially of the fornix conjunctiva. I have seen 3 such cases labelled 'early ocular pemphigus'. It is most important for the ophthalmologist not to imply the diagnosis of benign mucous membrane pemphigoid because this carries such an incomparably worse prognosis than all the other scarring conditions, except perhaps epidermolysis bullosa which I have not personally observed.

(3) *Management:* In the first place benign mucous membrane pemphigoid must be separated from the rest in assessing the results of treatment. In one proven case topical steroids were able to suppress the occurrence of ulcerative lesions in the eye over a period of two years before death from cancer. They were quite ineffective, however, in preventing shrinkage and symblepharon following previous ulcerations and at times they had to be used at fifteen-minute intervals.

Secondly, it is essential to recognize the presence of a keratoconjunctivitis sicca complicating any of the scarring diseases; it is often very rewarding to occlude the canaliculi, and the use of tear substitutes is essential.

Thirdly, it is worth remembering that considerable comfort may come from instructing the patient in the daily toilet of the ocular prepuce, for removal of the irritant keratinized smegma-like material which accumulates on the keratinized plaques which follow the scars of erythema multiforme may give great relief.

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Mr Frederick Ridley (*London*)

The Role of Contact Lenses and Shells

In pemphigus the lacrimal gland ducts may be occluded and this may lead to deficiency or absence of tears. Localized lesions in the conjunctiva lead to local scarring while deficiency of tears may give rise to shrinkage of the whole conjunctiva by a process of drying-out whereby the surface becomes wrinkled. This process of wrinkling seems to be rather like the closing up of the bellows of a camera. For this reason incision of the shrunken conjunctiva is to be avoided since the process of healing makes subsequent expan-

sion of the conjunctiva impossible. Shrinkage may go on until the conjunctiva bridges directly from the limbus to the lid edges, the globe, otherwise free to move, becoming anchored. The corneal epithelium is now stripped off and shrinks, so that in an extreme case we may have only a tiny central area of corneal epithelium. The last stage is for this central area to be stripped off when the globe becomes entirely free behind an operculum of shrunken conjunctiva and a residuum of corneal epithelium filling the palpebral fissure. This has been demonstrated by passing a probe infratemporally through the skin down to the sclera and demonstrating that it could and would be passed perfectly freely in front of the globe and behind the translucent operculum in the palpebral fissure. When there is only a small adherent area of epithelium we do not, I think, appreciate that this alone can regenerate transparent corneal epithelium as distinct from conjunctiva. Attempts using facial splints, to recover these very late cases have been unsuccessful but expansion of the fornices and some clearing of the keratinized cornea have been achieved.

Apart from improved visual acuity the contribution contact lenses and shells can make is first to hold open the fornices preventing contraction and adhesion in the subacute stage. They cannot be worn as a rule in the acute stage of the disease. When the disease is quiescent lenses should always be fitted and are usually worn very well, all-day wear being the rule. Continuous wearing is not unusual. Under these conditions it is probable that visual acuity need not deteriorate over the years at all. If the eyes have any natural tear secretion this may be adequate when evaporation is prevented by the contact lens. If the eye is dry, instillation of drops of sod. bicarb. 2%, Ringer-saline 0·6%, methyl cellulose or artificial tears may be necessary but this is a simple thing to do. Once all-day wear is established any discharge ceases, the cornea often clears steadily over several months, vascularization subsides, the eye becomes quiet and the fornices reform to a considerable extent by re-expansion of the contracted conjunctiva now permanently wetted. If the case relapses every effort should be made, preferably as an in-patient, to keep contact shells in the eyes as much as possible because if this is not done contracture occurs with frightening rapidity. In that case the patient should be refitted as soon as possible.

We have fitted several patients with old trachoma in whom a similar problem is seen.

The mechanics of contact lens fitting are the same in all these cases: to protect the eye from drying; to separate the conjunctival surfaces and to afford a mechanical barrier to irritation of the globe and cornea by ingrowing lashes, inturning lids or rough tarsal plates; and so to secure freedom from discharge and comfort for the patient while leading to a steady clearing of the cornea in most cases. All these cases should be fitted if at all possible. As an example, a patient has been back at work with 6/24 vision in each eye for six years, who during the previous six years was on the Blind Register: in another 6/18 vision is still present after twenty-four years of contact lens wearing.

Summary: Old people with active lesions and wet eyes are difficult to fit and tend to do badly. They often have good visual acuity and so derive no immediate reward from contact lenses. Patients in the quiescent stage following these diseases in early life – and usually with dry eyes and corneal involvement – do very well. Apart from increased visual acuity, freedom from discharge and complete comfort are achieved at once and the patient's lot may be improved dramatically.

Sir Benjamin Rycroft (*London*)

The Surgery of Ocular Pemphigus

Patients with eye complications of the bullous dermatoses such as occur in the late stages of chronic benign pemphigus and of erythema multiforme bullosa or Stevens-Johnson syndrome present a definite pattern of symptoms and clinical signs. Such patients complain of failing vision, irritation of both eyes and often dryness together with an absence of tears. Frequently there is a hoarse voice, a sore mouth and a story of 'blisters' on the skin.

The essential ocular lesion is a subconjunctival hyperplasia with marked increase of vascularization. In the palpebral conjunctiva this sometimes leads to the formation of a bulla although the ophthalmologist rarely has the opportunity of seeing such an example since the bullæ are transient. The bulla ruptures, a symblepharon remains and over the passage of time many similar adhesions are formed. Eventually the ultimate effect of the symblepharon is to unite the lid and globe firmly together and to invert, by secondary contraction, the lashlines so that the lashes irritate the cornea and produce ulceration. Coincidentally vascular tissue spreads across the cornea and obstructs vision. The lacrimal ductules and the orifices of the lacrimal puncta are usually occluded by scar tissue and finally xerosis sets in leading to total opacification of the cornea with keratinization and absolute fixation of lids and globe. Fortunately for surgeons the pathology of ocular pemphigus shows that the lesion is largely superficial and occupies a distinct plane. It is interesting to note how this granulation tissue can be peeled

off the cornea to leave a relatively normal appearance underneath.

The clinical signs therefore are (1) trichiasis and entropion, (2) corneal scars and vascularization, (3) symblepharon and ankyloblepharon with conjunctival and corneal xerosis, (4) lids-globe fixation.

TREATMENT

Ocular pemphigus may be divided into a moist and a dry form.

The Early or Moist Form

In this condition the cornea still receives some lubrication though it is grossly inadequate: surgery can do much to improve vision and a contact glass is of vital importance to preserve the scanty moisture on the corneal surface by preventing further evaporation. One sound principle is that the minimum of surgery should be undertaken. In earlier years it was our custom to carry out extensive reconstruction of the conjunctival fornices by free mucous membrane grafts but it is quite clear that in several cases the result of this surgery merely aggravated the vascularization and led to further cicatrization with complete failure.

The plan of treatment which is now advocated is as follows:

(1) *Transcutaneous linear tarsectomy:* This is a routine procedure which is carried out on upper and lower lids with the object of everting the lashes from the cornea. A wedge of tarsal plate is excised along the whole length of the lashlines by the transcutaneous route. Alternatively, the Van Milligan operation is occasionally used but in this operation the autograft is also of potentially pemphigoid mucous membrane.

(2) *Strip peritomy:* A circumferential strip of conjunctiva surrounding the entire cornea is removed measuring 4 mm in diameter and the sclerotic is laid bare. Large trunk vessels are carefully dissected out and all vessels are cauterized on the conjunctival edge. The result of this procedure is that a bare avascular area surrounds the cornea and is a temporary barrage to the ingrowth of adventitious conjunctival vessels. It is of course only temporary because later the conjunctiva grows across, but at any rate it does leave time for corneal lesions to heal as for example after a keratectomy.

(3) *Superficial keratectomy:* This procedure is undertaken to clear off redundant and excessive adventitious vascular tissue from the surface of the cornea and it is surprising how easily it is peeled off and what an excellent surface is left behind. In our experience a lamellar corneal graft is rarely required on account of the relatively normal corneal tissue underneath.

(4) *Fornix incision:* The fornices nowadays are dealt with simply by division of the symblepharon sufficient to permit the fitting of a permanent contact glass. No attempt at reconstruction of the fornices is made as the final result is usually worse than the initial condition by virtue of increased contracture. When sufficient depth of fornix has been obtained by a simple incision and cautery of bleeding points, a large shell of the Walser type is inserted and worn permanently. Some cases are so badly contracted that this is not possible and then the corneal type of contact lens has to be used, and in some examples has proved of great value.

(5) *Local treatment* is by the use of artificial tears and steroid drops: these are routine in every case. In our experience general steroid therapy has proved of considerable value in the control of the disease and with the increasing age of the patient there is a tendency for the severity of the disease to diminish.

The Dry or Late Form of Ocular Pemphigus

For this condition surgery offers very little hope. If the condition is severe and true xerosis has set in it is our experience that keratoplasty merely repeats the original pathology and corneal grafts readily become opaque by lack of moisture and adequate lid coverage. It is true that the delay in the deterioration of the graft can be prevented by the use of a contact shell and it is probably correct to say that in every corneal graft for ocular pemphigus a permanent contact glass is essential. Strampelli (1958) gave the results of Stenson duct-conjunctival anastomosis after ten years. He considered that the operation was not successful even though the eye was moist. Xerosis was not improved and a lamellar graft became xerotic under these conditions. On the other hand, Segal (1957) concluded that if transplantation does not cure the condition it is the most effective method advocated so far for an incurable state of affairs.

May's case (*Time Magazine* 1958) was regarded as successful because 'when Dougherty, the patient, heard and smelled the lunch wagon the flow of saliva into the conjunctival sulcus was copious'!

Finally, there is no doubt that recently the outlook for patients suffering from ocular pemphigus is much better, not because of surgery but because of the modern improvements of contact lenses.

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Section of Anæsthetics

President

Professor R F Woolmer VRD FFA RCS

Meeting November 4 1960
at the Royal College of Surgeons
Lincoln's Inn Fields, London

Paper

Anæsthesia for Emergency Surgery in Children [*Summary*]

by Robert M Smith MD (*Boston, Mass.*)

Numerous problems are associated with so-called 'emergency' operations on young patients. These can bring tragic results unless the dangers are recognized and special precautions are observed to prevent them. First, it is a common fallacy to hurry with these unscheduled cases, to cut corners either through impatience, carelessness, or an erroneous belief that haste is all-important. Actually, the term 'emergency' is rarely justified, and most situations are improved if treated with calm thoroughness rather than headlong speed. In this way other important conditions will not be overlooked, such as multiple injuries in an accident case, or diabetes complicating an emergency abdominal condition.

Fear on the part of the young patient is an important factor that can introduce serious physical as well as emotional complications. A bleeding, screaming child makes a poor subject for anæsthesia, and to bring such a patient to the operating floor without proper time to calm and pacify him is brutal and unsafe. The methods employed are of less importance than the results. The three important factors are adequate pre-operative sedation, the personality of the anæsthetist, and a skilful technique of induction of anæsthesia. A careful, unhurried examination of the child is essential; the frightened young child is best premedicated with rectal tribromoethanol or rectal Pentothal; morphine is useful in older children.

The problem of the full stomach is well known and is frequently encountered. Although many different approaches have been advocated, experience has narrowed the choice considerably. Few anæsthetists now rely on waiting a specified time or on attempting to empty the stomach by lavage or induction of vomiting. If an injury is sustained within two to three hours of a meal, undigested material may be vomited up to twenty-four hours later. The induction of vomiting by making the child retch may not empty the stomach completely, and lavage with a wide-bore tube will remove only liquid or semi-liquid material. It is not practicable to intubate a conscious child. While some favour a 'crash' induction with Pentothal and a relaxant immediately followed by intubation, this is dangerous in the presence of abdominal distension, and induction with cyclopropane or nitrous oxide and oxygen is preferable, followed by intubation when a sufficient depth of anæsthesia has been reached. It is agreed by most that local anæsthesia is often advisable, and that if general anæsthesia is indicated an endotracheal tube should be employed, and *left in place until the patient is awake*. Suction equipment, mouth gags, and a bronchoscope should always be available.

Other problems include the child with peritonitis and high fever, the child with acute respiratory obstruction, and the newborn infant with intestinal obstruction. Suitable apparatus and a clear plan of action are essential if success is to be expected.

When children are admitted to the hospital with peritonitis, fever of 104° F to 105° F and signs of dehydration and toxicity it is best to delay operation for as much as four to twenty-four hours while steps are taken to control the fever and institute antibiotic and fluid therapy. Since adoption of this regime, serious complications from hyperthermia have been eliminated.

Usually aspirin per rectum, or skin-sponging with alcohol will lower the temperature. If rapid cooling devices of the Therm-o-rite type are used, the temperature will often fall before the child's condition justifies operation. Additional time should be allowed in such cases. Atropine should be withheld until immediately before operation, and then given by vein in slightly reduced dosage.

Newborn infants, especially those with intestinal obstruction, present difficult problems. Very weak infants often may tolerate all of the operation under local infiltration anæsthesia, while some will need nitrous oxide or cyclopropane only during peritoneal closure.

For many abdominal procedures and all intrathoracic operations (tracheo-œsophageal fistula, &c.) general anæsthesia is required. For those, awake intubation followed by cyclopropane by to-and-fro method has been satisfactory.

In exomphalos (omphalocele) a similar technique is used. Relaxants may be helpful, but due to the possibility of post-operative restriction of respiration in this condition it is preferable not to risk further depression from prolonged action of a relaxant. This danger is accentuated when infants become cold during anæsthesia. It is always of critical importance to watch these patients with extreme care following operation.

During operations on neonates it is essential to keep the infant warm. The limbs are wrapped, and a rectal thermistor registers the temperature continuously. Blood pressure is measured with a narrow cuff designed for neonates, and read by the swing of the Tycos needle. Pressures of 75–90 systolic are reasonable if maintained. A precordial stethoscope is used on all patients – unless the entire chest is inaccessible. Then an œsophageal stethoscope is employed. This is easily constructed by cutting 3 extra holes in the terminal 2–3 cm of a 12 to 16 urethral catheter, then covering the holes by drawing a thin latex (Penrose) tube over the catheter end. The catheter is then substituted for the bowl of a standard binaural stethoscope and passed down the œsophagus until heart and breath sounds are audible.

In the child with respiratory obstruction the airway must first be re-established by endotracheal intubation or the passage of a bronchoscope. In the United States a tracheostomy stab with a trocar has been tried, but it is dangerous, because the trocar point may damage other tissues and fail to enter the trachea. Several deaths have been reported as a result of its use. Tracheostomy should not be attempted until after the patency of the airway has been ensured. In the Pierre-Robin syndrome (macroglossia, micrognathia, cleft palate), sudden respiratory obstruction may occur. The important features in treatment are intubation followed by tracheostomy, and then careful nursing, often in the prone position, and sometimes for some months.

It is essential not to approach these problems with any fixed ideas, but to keep an open mind, treating each case on its own merits.

DISCUSSION

Professor T C Gray (Liverpool) asked Dr Smith whether he thought that in view of the disproportionate amount of work that respiration entails in tiny infants it was not better for them, when submitted to the strain of operation, if the anæsthetist took over this burden and controlled respiration.

Dr Smith said that these infants apparently had no discomfort; if they were restless or appeared to be in pain a general anæsthetic was desirable, but he felt that spontaneous respiration was better than controlled; there was less interference with the circulation, and he preferred to preserve intact as many faculties as possible.

Dr Robert Cope (London) agreed with Dr Smith, but wondered whether closure of the abdomen without muscular relaxation was really safer than controlled respiration in these cases.

Dr Smith replied that he considered that it was a matter of degree: if there was a struggle, then relaxation was desirable, but if a tumour was removed, it was not usually necessary. He emphasized that some of the surgery might last several hours. It was necessary to consider the conditions obtaining at the time.

Meeting December 2 1960

President's Address

Information Please

by Professor R F Woolmer VRD FFA RCS (*London*)

When the University of Bristol, to which I was until recently attached, was a University College aspiring towards a Royal Charter, discussion arose as to a suitable motto. The most popular proposal was a Latin tag meaning 'Knowledge is Power'. The Bursar, harassed by the difficulty of making both ends meet, wryly suggested that a slight twist in the wording would make it more appropriate, and that it should be rendered 'College is poor'. The more orthodox version was, however, adopted; and I suggest that it is a good motto, not only for a University, but also for a practising anæsthetist.

The word 'knowledge' can have various shades of meaning. It can be equivalent to 'learning' and this is attested by its substitution for that word when Pope's line, 'A little learning is a dangerous thing' is misquoted, as it usually is. Or it can mean a collection of information. The desirability of anæsthetists being learned, in the academic sense, needs no arguing. What I want to discuss here is the desirability (which should be rated no lower) of their being knowledgeable in the sense of being well informed – well informed about the

steps of the operation in progress, well informed about all the drugs that are being used, and above all well informed about the state of the patient.

I do not believe that anybody, however experienced, can be fully informed about the state of the patient merely by looking at him. Close observation is vitally important, but our unaided senses cannot provide us with as much information as we ought to have. The thorough examination of the patient before operation, and the collation of the appropriate biochemical and physiological examinations, is the only firm basis on which measurements made during surgery can rest; and we must do our best to get our conditions of work adjusted so that this examination does not have to be skimped; but I am more concerned at the moment with the means available for keeping ourselves accurately informed of the state of the patient during anæsthesia. What do we need to know? The amount of information needed, and its character, will obviously vary according to circumstances. We require less information to take adequate care of a healthy patient undergoing herniorrhaphy than we do of a blue baby having a Blalock's operation.

Nevertheless, even in the simplest case, a mass of information *is* being conveyed to the anæsthetist through his unaided senses. The general appearance of the patient, the colour of his skin, the nature of his breathing, the character of his pulse and the tone of his muscles—information on all these flows in a constant stream through the sensory channels of the observant anæsthetist, and goes some of the way to giving him command of the situation.

It is perhaps a characteristic of artists that they observe things, and a characteristic of scientists that they measure things. The handling, by a trained mind, of the qualitative information I have mentioned constitutes the art of anæsthesia, the firm base on which any scientific edifice must be built. All this information, and a great deal more, can in addition be presented in quantitative form by the appropriate aids to observation; and it is the collection of information in this form, its handling, and the response to it which make up the science of anæsthesia, a science as yet in its infancy.

The simplest piece of information which we are accustomed to handle numerically is the frequency of the pulse. To quantitate this, our senses have to be aided by a device for measuring time – a clock or a watch – which mechanically is quite a complex instrument, though familiarity makes us look on it as simple. The question of what is simple and what is complicated is often clouded by confused thinking, as Professor W W Mushin pointed out some years ago. Medical men are often unwilling to use electrical or mechanical equipment for clinical application on the grounds that it is complicated. Yet a doctor who refused, for the same reason, to use a motor car or a watch would be regarded as a little weak in the head. When faced by this argument people often take refuge in the idea that the more apparatus there is in use the more there is to go wrong. This of course is perfectly true; but to deny oneself the advantages of a piece of equipment because it may not function perfectly all the time is logical only when its failure would endanger life.

This is a consideration often met with in industrial control systems and in the aviation industry; and it has led to the principle of 'failure to safety'. According to this principle, apparatus is so designed, by the incorporation of interlocking devices, by the duplication of components, or by the provision of warning systems, that failure of a part will not result in disaster. An example familiar to anæsthetists is the operating room light with its auxiliary lamps, fed from an independent source, which comes on automatically and immediately on the failure of the main lamp or its power supply. The principle is also incorporated in the better examples of mechanical respirators. Increasing reliability of components and the elaboration of the 'failure to safety' principle, which are the fruits of development in control systems for aircraft and for guided weapons, can now confer on most of the instruments that we are likely to use a reliability comparable to that of the motor car and the watch. The possibility of their failure, while it should never be neglected, is no longer a valid reason for denying ourselves the use of instruments that will increase our ability to make scientific observations. A properly designed instrument should present the appropriate information to the operator in a form in which it can be used immediately and without further computation, and here the anæsthetist's watch – simple to use and reliable though it is – falls short of the ideal. Taking the pulse rate demands the undivided attention of the anæsthetist for not less than 15 seconds; and it is remarkable how often that particular 15 seconds will be chosen by the surgeon to request that his brow be mopped or the light be adjusted.

It is the very versatility of the human sensorium – the vast range of information to which it will respond – that makes it susceptible to interference of this sort. This can be eliminated, or at any rate reduced, by mental concentration – by rendering the sensorium insensitive to all signals but those in a particular channel; but such sharp focusing of the attention, which is analogous to sharp tuning in a radio receiver, is difficult for the human mind and may well be dangerous.

The logical solution, according to *information theory*, is to set up an independent channel for

information about the pulse rate, with a specific sensing device at one end and a read-out device at the other end, by which the information in its proper form may be stored and displayed. The attention of the anæsthetist can then be given to the display when convenient. Such an arrangement, uncommon in operating rooms, is called a cardiotachometer. The sensing element here may be a carbon microphone which responds to the pressure of the pulse wave as do the sensory nerve endings in the palpating finger, or it may be a device responsive to a sharp swing of electrical potential detected by the electrocardiogram, or it may respond through a photocell to the rhythmic changes in translucency of the tissues which accompany each heart beat. However the pulse is detected, its rate is quantitated in most cases by measuring the pulse interval. In place of the balance wheel of the anæsthetist's watch, the standard with which this interval is compared is the time required for an electric charge to leak away from a capacitor through a resistance. If comparison with this fixed duration shows the pulse interval to be half a second, the pulse-rate will clearly be 120: if the pulse interval is $\frac{3}{4}$ second the rate will be 80, and so on. The comparison is made electrically for successive pulse intervals, the average of several is determined by an integrating circuit, and the result displayed, in terms of beats per minute, on a dial for the anæsthetist to read when convenient.

All this sounds a little complicated, but is in fact a simple example of electronic instrumentation. If the natural process of the anæsthetist's fingers feeling the pulse, his eyes looking at his watch, signals passing by separate sensory channels to a control centre in the brain, and integration taking place there – if this process were described in detail in terms of information theory it would appear much more complicated.

It is clear from this example that if the anæsthetist's sensorium is to retain its full range of versatility, so that he can survey the patient as a whole, a number of separate channels for numerical information will have to be set up, each with its appropriate form of display. The forms in which such information can be displayed to the human operator by measuring devices are capable of wide variation: their output may be arranged to stimulate any one of the five senses. The senses of sight and hearing are the ones normally chosen by instrument designers because they are dominant in *Homo sapiens*. A pointer moving over a dial, a flashing light or a warning hoot are readily appreciated. If dogs took measurements, they would doubtless arrange for the output of their measuring devices to take the form of an olfactory stimulus, which would pose some pretty problems for the designer.

The output of a pulse detector may be arranged to give an auditory signal or a visual signal or both. Each pulse beat can be caused to flash a light *and* emit a bleep on a loudspeaker. In this way an alternative input channel to the anæsthetist's brain is made available and can be used when the visual channel is already occupied by such activities as brow-mopping, light-adjusting or record-keeping. This type of display of the pulse detector's output differs from the visual display in an important respect. It is omnidirectional, so that it reaches the surgeon and everyone else in the operating room who happens to have ears.

It is part of information practice to decide whether a display should be unidirectional or multidirectional; and there are several things which influence our decision in this. It is the business of the anæsthetist to protect the surgeon from worry and distraction. An auditory output from a pulse detector when the heart is faltering or when the instrument is behaving erratically (which is not unknown) may be very disturbing. However, it needs but little ingenuity to separate the auditory output from the visual one, and to cause the auditory output to bleep, with impeccable regularity, at whatever rate will maintain peace of mind of the surgeon and the operating team – though it may be embarrassing to the anæsthetist if he has to pronounce the patient dead when strong regular bleeps are still being broadcast through the operating room.

The most useful single item of quantitative information which is available to every anæsthetist is the blood pressure; and it is a matter for reproach that so often, in Britain, anæsthetists fail to take advantage of it. The excuse often given is that sphygmomanometry distracts the anæsthetist from proper attention to the patient as a whole. The stethoscope diaphragm may become displaced. The surgeon or the assistant may lean against the cuff. The length of the stethoscope tubing may not permit free movement of the head. The mercury column or anaeroid dial may be in an awkward position. The squeezing of the bulb is a nuisance. All these inconveniences can be avoided with a little ingenuity. The stethoscope can be replaced by a peripheral pulse detector, the cuff can be inflated at a touch with cylinder gas, and the meter can be properly sited. With these simple modifications sphygmomanometry need be neither inconvenient nor distracting. For those who require, and can afford, something more sophisticated an automatic blood pressure follower is available and this has the additional advantage that it can present the information graphically.

This leads us to consider whether the items of information about a patient which come in during the course of an anæsthetic should be indicated in an evanescent form and then discarded, or

whether they should be recorded, either automatically by an instrument or manually by the anæsthetist. The keeping of records during anæsthesia is a neglected art in this country. Various excuses are made for this. It is said that the keeping of records distracts the anæsthetist from proper attention to the patient. It is said that records are not likely to be kept accurately, particularly when things are going wrong which is when they are most needed. It is said that the busy anæsthetist does not have time, between cases, to complete his record cards.

None of these excuses is really valid. It is only by keeping a record in graphic form that various events, such as changes in blood pressure or pulse rate, can be related to their causes. This is true not only for changes in the cardiovascular system, but the respiration also. The anæsthetist ought to have quantitative information about this and he needs it whether the respiration is spontaneous or controlled.

An increasing realization of this had led to a widespread demand for some means of measuring ventilation during anæsthesia. This demand is being met, in part, by instruments such as the Wright respirometer, the Dräger and Monaghan volume-meters, the Elam ventilometer and the dry gas meter. None of these meters, however, provides the anæsthetist with information in a really useful form. They merely measure the volume of gas passed through them, whereas what the anæsthetist is interested in is the volume passed per unit time, or the minute volume. This, in the language of information theory, is the first time derivative of the volume. It can, of course, be obtained in a rough and ready manner if the anæsthetist possesses a watch and the ability to divide the volume passed by the elapsed time. But this will merely give the mean volume during the period of measurement. It will not reveal fluctuations during that period; and the process of measuring two quantities, volume and time, and dividing one by the other has to be carried on continuously if changes in ventilation are to be appreciated. That, of course, is impossibly tedious and distracting; and this accounts for the poverty of the information which the anæsthetist actually derives from a volume-meter.

What is needed is a differentiating ventilometer which will automatically measure the two quantities – time and volume – and do the sum, and go on doing this continuously, so that it can present its information in the form of a continuous record of the instantaneous minute volume. Two machines for doing this have been devised. One, which indicates only, is already available. The other, which records, will be available soon.

The anæsthetist who is in possession, throughout an operation, of a graphic record showing changes in blood pressure, pulse rate and ventilation is on the way to meriting the description of a well-informed observer. During inhalation anæsthesia, however, it is also desirable to know the composition of the respired gas mixture. Though we have a good knowledge of the nature of its components, we are in most cases very ignorant of their concentration. Considering the potency of some of these components, this is rather shameful.

The quantitative analysis of a complex gas mixture has in the past been difficult and slow. By established chemical methods it would be possible to determine that the patient had been given an overdose of a volatile anæsthetic in time to announce it at the Coroner's court, but not in time to prevent the catastrophe.

Ideally the anæsthetist should be continuously supplied with information about the concentration of every component in the respired gas mixture. Until recently, this ideal seemed quite unattainable; but advances in physical methods of gas analysis, and particularly in gas chromatography, are bringing it within reach. It is perhaps not too much to hope that in a few years' time the means for continuous analysis of the respired gas mixture and for the rapid determination of the concentration of volatile anæsthetics in blood and body tissues will be widely available.

Since the anæsthetist is usually responsible for maintaining the patient's circulating blood volume, it is important that he should have information about blood loss. Precise knowledge of this is practically never available. The rough estimates made from looking at the swabs and the sucker bottle are notoriously inaccurate. Careful swab-weighing gives much more reliable information, but it is tedious and has errors of its own, and the result of the measurement requires conversion from weight to volume. The form in which the anæsthetist wants the information is: 'Up to this minute the patient has lost so much blood. So much has been replaced, giving a positive or negative balance of so much.' Up-to-the-minute information, in terms of the amount of blood lost, can be furnished by the hæmoporrhometer. This consists of a tank of water, suitably agitated, into which swabs and sucker output are received. The electrical conductivity of the water is dependent on its electrolyte content, and thus varies with the amount of blood added to it. Conductivity is continuously measured by a simple bridge circuit and the result is expressed on a dial directly in terms of blood loss. Saline-soaked swabs must not be used, as the machine cannot distinguish saline from blood; and, of course, the machine can measure only what is put into it. The hæmoporrhometer is undoubtedly an advance but unfortunately costs several hundred pounds. For those who like to think in terms of automation, it

would not be difficult to connect the output of the hæmoporrhometer to a servo-operated pump and control valve, so that blood replacement would be automatically equated to blood loss.

The electrocardiograph provides information which is valuable in a rather limited field; and its value increases in proportion to the education of the anæsthetist. In contrast to what I have said about certain other types of information, an indicating instrument – an oscilloscope with a long persistance phosphor – is usually more appropriate than a recording instrument. The oscilloscope trace is easier to see, and the recording instrument has the disadvantage that the volume of redundant information it puts out may be overwhelming. If we can afford to have the best of both worlds we will use an oscilloscope to display the unimportant information and a recording instrument to preserve the small proportion which is worth keeping.

Considering the importance to anæsthetists of the central nervous system, it is remarkable that quantitative information concerning its activity is so little used. The main reason for this is that for most anæsthetists the value of such information as can be obtained is incommensurate with its cost. Electroencephalography is not a very good means of providing the sort of quantitative information which the anæsthetist needs. Automatic frequency analysis of the output makes the information more useful, but at much greater cost. Even without frequency analysis, the changing pattern with increasing depth of anæsthesia is fairly obvious in favourable circumstances. With ether, the correlation between the EEG level and the concentration of anæsthesia in the blood is good in humans; but with nitrous oxide, the only agent for which a good correlation would be really useful, it is rather poor, and hopes that the EEG might provide us with the information which would enable us to keep the patient just below the level of consciousness with certainty have been disappointed.

Hypoxia, hypercarbia, and other biochemical changes may also confuse the picture; though if other factors are held constant the change in pattern induced by hypoxia may be used as a warning of threatened brain damage during cranial surgery and extracorporeal circulation.

Accurate information about the patient's temperature is vital to the practice of induced hypothermia. This information can readily be furnished by electrical instruments, such as thermistors, thermocouples or resistance thermometers. But the anæsthetist also needs to know the rate of change of temperature – its first time derivative. This can, of course, be obtained by plotting the temperature against time on linear co-ordinates and noting the slope of the graph (Fig 1). If the rate of change is constant, the curve

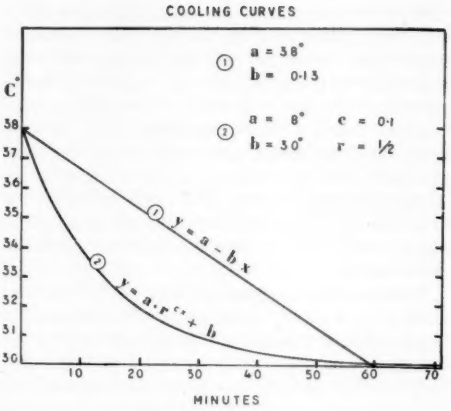

Fig 1

will be a straight line. Such a curve is shown in the upper part of the figure and can be expressed by a simple linear equation of the form $y = a - bx$. No one would be happy, at the forty-fifth minute, with the state of affairs represented by this curve, even though the temperature is still $1\frac{1}{2}°$ above the desired level. What is needed, clearly, is a much more gradual approach to the final temperature, in order to avoid overshoot, and a rapid initial fall to minimize delay. Such a course is shown in the lower curve; and obviously the anæsthetist who is aiming at a final temperature of 30° C would be very satisfied with the situation at the forty-fifth minute. In this curve the slope, or the rate of cooling, at any instant is less than it was during the preceding instant. The equation of this curve is an exponential one of the form $y = a.r^{cx} + b$. The two variables, x and y, are time and temperature respectively, as in the first equation. Of the four constants, b is the temperature aimed at, and a is the number of degrees through which it must fall. I have put these values at 30° C and 8° C respectively. c is a constant which controls the time scale. Here I have given it the value of 0·1, so that the process takes about an hour. The effect of increasing it would be to compress the time axis, and make the cooling quicker. r is a fraction governing the rate at which the rate of cooling diminishes with time (the second time derivative). Here I have made r equal to $\frac{1}{2}$, so that the rate of cooling, after 10 minutes, is half what it was at the start. By the 20th minute, it is halved again, and so on. Other values for r, giving different rates of decrease of rate of cooling, are of course possible.

This is the type of equation which would be applied to the control of industrial processes, and its application to the control of hypothermia is obvious. What the informed anæsthetist should do is to decide on the curve he wants – and he will

presumably choose one similar to this – and then make arrangements to follow it. Given a cooling unit of sufficient power (and modern refrigerating techniques can easily provide it) this is theoretically quite easy. The temperature and its first time derivative (its rate of change) at any moment is compared with those required by the curve, and the rate of cooling is increased or decreased to counteract any deviation. This is the sort of thing which is done much better by servo control techniques than by human agency; and it is not difficult to set up an automatic cooling unit which will perform this function. The curve represented by the selected equation will then be followed, and the desired temperature will be attained at the predicted time without danger of overshoot. This is merely an example to show how a simple application of information theory may be useful in anæsthetic practice.

All those who are engaged in the practical teaching of anæsthesia are aware that during most of the time they spend in the operating room with a pupil the rate of transfer of information from teacher to taught – the rate of learning – is lamentably slow. During the hour or so that is occupied by an uneventful colporrhaphy, teacher and student sit side by side. The more energetic teacher may let fall a few pearls of wisdom: the livelier student may ask a few questions; but after a while the tedium of the affair exhausts their powers of communication, and they fall silent, each wrapped in his own thoughts. It is only when the oxygen runs out, or the bobbin of the cyclopropane rotameter is found to be at the top of the tube, or the entire apparatus disintegrates in an explosion, that information is injected into the student quickly. If something of this sort happened during *every* anæsthetic, the student (if he survived) would mature very quickly, and the time and cost of training him could be materially diminished. Though some teachers do indulge in such tricks as surreptitiously closing a cylinder valve, it is difficult to produce emergencies to order in real life. But if a suitable technique were elaborated they could be quite convincingly simulated. A parallel problem exists in the aircraft industry, and is solved by the use of aircraft simulators. Such a simulator is a facsimile of the control cabin of an aircraft. Though it never leaves the ground, it can be made to roll, to pitch, and to yaw, and its instruments can put out information corresponding to a blind landing in fog, or to an engine failure in mid Atlantic. In this way a pilot can be given, in a few hours, and at little cost, experiences which he might not otherwise acquire in a lifetime. It should not be beyond the bounds of human ingenuity to design a patient simulator for the training of anæsthetists. It would be made to look as lifelike as possible.

The tissues would be subtly translucent; and an inner light of adjustable colour would produce cyanosis, pallor or plethora at will. A rubber tube within the soft tissues of the arm would represent the brachial artery, through which fluid could be pumped at a pressure and rate which could be varied by the instructor. A pump connected to the chest would simulate whatever form of respiration was required. Alarming electrocardiographic patterns could be stored on magnetic tape and fed to an oscilloscope, and the blood loss recorder could be made to indicate a disastrous situation, which, however, could be retrieved by the trainee if he did all the right things.

Such a piece of equipment would be elaborate and expensive, but it would provide a means of conditioning a student to react to an emergency without putting human lives in jeopardy. I am not suggesting, of course, that such a patient simulator should be a substitute for conventional methods of teaching; but it might be a useful supplement to them.

It is sometimes said that it is a bad thing to rely on instruments, and that there is no substitute for the clinical judgment of the trained anæsthetist, guided by his accumulated experience and skill, his olympian calm unruffled by anything so mundane as taking measurements. The people who hold this view would not trust themselves to an airline pilot who scorned the use of navigational aids. When they themselves are the pilots, conducting their passengers on the journey towards the frontiers of death which is anæsthesia, they too should make use of all the navigational aids that can be provided. The policy of 'reliance on unaided observation backed by experience' is often a cloak for laziness. Clinical judgment and experience are indispensable, but by themselves are not enough. I defy any anæsthetist, however experienced, to tell consistently, by his unaided senses, within a 25% margin of error, the systolic blood pressure or the pulse pressure, the minute volume of ventilation, the inspired concentration of volatile anæsthetics, the excess or deficiency of the circulating blood volume, or the deviation from normal of the body temperature.

Yet we owe it to our patients to be precisely informed on these points; and we should regard such instrumental aids as we can obtain, not as substitutes for observation and clinical judgment, but as a means of extending and augmenting the sensory input on which clinical judgment must depend. Information and control must go together, and we cannot fully exercise the control required for mastery of the situation unless we are supplied with the information which is a prerequisite for it.

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Section of Pathology

President Professor Noel F Maclagan DSC MD

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President's Address

Changing Views on Jaundice

by Professor Noel F Maclagan DSC MD (*London*)

The problem of jaundice is one of special interest to pathologists since so much research has been done in all branches of pathology in relation to this one symptom. In view of important recent work it seemed appropriate to review the subject at this time, and also to look back a little at older views since there has been something of a cycle of opinion on jaundice during the last hundred years, and we cannot be entirely sure that the wheel has stopped revolving. I have been able to watch part of this cycle myself since I am old enough to have been taught about plugs of mucus as a cause of 'catarrhal' jaundice, to have heard quite a few misleading interpretations on the van den Bergh reaction, and to have witnessed the discovery and later the virtual elimination of homologous serum jaundice. I shall restrict this Address to work bearing upon the pathological nature of jaundice rather than upon particular diseases which may cause it.

Early Views

In attempting to trace the origin of any particular view one is inevitably driven back to older and older references, and it appears that a broad distinction can be made between the early writers who regarded jaundice either as a symptom or as a disease in itself and those who, particularly during the last hundred and fifty years, have been more concerned with the pathological causes of jaundice. Thus the famous aphorisms of Hippocrates (460 B.C.) include three of interest to us to-day: 'When jaundice supervenes in fevers before the seventh day it is a bad symptom unless there be watery discharge from the bowels. When in a case of fever jaundice occurs on the seventh, ninth, eleventh, or fourteenth days it is a good sign provided the hypochondrium be not hard; otherwise this is not a good symptom. In cases of jaundice it is a bad symptom when the liver becomes indurated.' It is not perhaps surprising that these dicta were not universally accepted, e.g. by Pliny (A.D. 77), and it is difficult for us to be certain what diseases Hippocrates had studied to reach these conclusions. Pliny was perhaps on safer ground in stating that jaundice was favourable when following fever, but deadly if followed by fever. In A.D. 70 Plutarch notes that jaundice is cured by gazing on the golden oriole, 'the bird appears to attract the disease to itself and averts its head and closes its eyes not, as some think, because it is jealous of the remedy sought from it, but because it feels wounded as if from a blow.' Incidentally, the Greek word for oriole is ἴκτερος, so that we are frequently guilty of perpetuating this picturesque legend. Other remedies somewhat later include the cooked juice of the plantagenet (Gilbert 1270), the administration of lion's gall (Magnus 1260), and of earthworms in ale (Wood 1639). A particularly attractive prescription, which reads to-day a little like an attempt at virus cultivation, comes from Burggrav (1611). He advised that an egg be emptied, filled with the patient's blood and sealed with fish glue. It was then put under a sitting hen for two weeks and fed to a pig or a dog; the disease was transmitted to the animal and the patient was cured.

17th to 19th Centuries

Writers such as Sydenham (1624–1689; *see* Sydenham 1848), Willis (1678), Morgagni (1682–1771; *see* Morgagni 1822), Blackmore (1727) and Fordyce (1777) described a bewildering number of causes of jaundice, but did not attempt any general classification – unless Sir Richard Blackmore's distinction between yellow and black jaundice can be accepted in this light. Conditions frequently associated with jaundice at this period were hysteria and mental disturbance, and one would like to be able to advance some plausible explanation for this. Somewhat later Saunders (1793) and Heberden (1806) came nearer to formulating general principles since they appeared to separate hepatic from non-hepatic causes. The latter records his scepticism as to hysterical jaundice of which he had not seen any examples.

The first real classification seems to come from Richard Bright in 1836, who recognized the following causes: (1) Congestion of blood in the liver, (2) obstruction of bile in the biliary ducts, (3) chronic change in the structure of the liver, and (4) inflammatory action of the liver. It is difficult to understand exactly what is meant by some of these categories since the third example is said to be 'usually due to excessive use of stimulating food and drink'. The fourth is listed as one of the common causes of jaundice and from his description would appear to include infective hepatitis.

A simplification was introduced by George Budd in 1845 who recognized only two types of jaundice: (1) Due to impediment of bile flow, and (2) due to defective secretion of bile in the liver. He based this simple and surprisingly modern conception upon the state of the gall-bladder and bile ducts at autopsy. The second group included gross diseases of the liver, fevers, poisons and mental shock, but he recognized familial cases of a condition which was almost certainly infective hepatitis and notes that they were usually mild but occasionally fatal. Work by Virchow in 1847 on bruising suggested the possibility of a third category of jaundice due to production of bilirubin outside the liver, so that at this time the possibility of an acceptable classification was present. Unfortunately, however, owing to various sources of confusion, Virchow later abandoned this conception and it was almost eighty years before these three types of jaundice became finally recognized.

A number of different classifications appeared during the rest of the nineteenth century, none of which would be considered acceptable to-day. The obstacles to understanding at this time arose mainly from doubt as to whether bile pigments could be produced anywhere outside the liver, a doubt which had two important results. Firstly, the idea of liver failure as a cause of jaundice became unpopular since, if it were the only source of bile, failure should not produce jaundice. Secondly, the conception of hæmolytic jaundice was difficult to establish, such cases being ascribed to excessive secretion of bile (polycholia). The various classifications of Frerichs (1860), Harley (1863), Murchison (1885) and von Ziemssen (1880) all reflected these difficulties. However, Osler (1892) produced an almost modern classification: (1) Hepatogenous or obstructive jaundice. (2) Non-obstructive jaundice, (*a*) due to suppression of liver function, (*b*) due to excessive formation of bile. He fitted satisfactorily into this classification many diseases such as acute yellow atrophy, malaria, pernicious anæmia and fevers, but attributed the effects of poisons entirely to hæmolysis. This last view was widely accepted at this period when the direct action of poisons on the liver was not recognized.

Osler appears, however, to have been the last writer to maintain this point of view in the face of the new experimental evidence, produced by the now famous experiments on the goose of Minkowski & Naunyn published in 1886. But for the danger of a confusion of species one might almost refer to these geese as red herrings. These workers showed that in hepatectomized geese no overt jaundice occurred after the experimental induction of hæmolysis by gassing with H_2S. This finding was regarded by many as the final proof that bile pigments could only be formed in the liver, and as a logical consequence both suppression of liver function and overproduction of bile were abandoned as possible causes of jaundice. This work also appeared to harmonize perfectly with Virchow's earlier description of the plug of mucus as a cause of biliary obstruction in 'catarrhal jaundice' (1865), and it was therefore accorded what appears to us now an undue significance. Thus we find that the classifications accepted a few years later were those of Sir Humphry Rolleston in 1905 and William Hunter in 1908. These writers recognized only: (1) Simple obstructive jaundice, and (2) toxæmic obstructive jaundice, the latter including all the non-mechanical varieties. It was specifically stated at this time that 'all jaundice is obstructive', and that 'it is very doubtful if any forms of jaundice can be attributed to suppression of hepatic function'. These opinions were also held by Eppinger (1908) and remained virtually unchallenged for nearly twenty years.

The Modern Period

The next major advance was the work of Sir John McNee (1923) which really established the classification of jaundice accepted to-day. McNee, working in Aschoff's laboratory, had repeated the experiment of Minkowski & Naunyn on the goose referred to above. Although obtaining similar results McNee discovered that the goose was peculiar if not unique in having nearly all its reticulo-endothelial cells in the liver so that it constituted a special and rather misleading example. The accuracy of his view was rapidly confirmed when Mann and his colleagues in 1926 published their work on experimental hepatectomy in dogs. They showed conclusively that in the dog, in contrast to the goose, the serum bilirubin regularly rose in animals surviving hepatectomy for twenty-four hours, and they were further able, by observations on arterial and venous blood from various sites, to prove that in dogs the bone-marrow was the main site of bilirubin production.

McNee was therefore on firm ground in distinguishing three main varieties of jaundice which he called: (1) Obstructive hepatic, (2) toxic and

Table I
Pathological Classification of Jaundice

Principal cause	*Nomenclature according to*			
	McNee (1923)	*Rich (1930)*	*Lichtman (1942)*	*With (1944)*
Excessive hæmolysis	Hæmolytic	Retention	Pre-hepatic	Production
Hepatocellular damage	Toxic and infective	Regurgitation	Hepatic	Retention
Mechanical obstruction of bile passages	Obstructive hepatic	Regurgitation	Extrahepatic	Lymphogenous

infective hepatic and (3) hæmolytic. We should indeed be grateful for this simplification of our ideas from which much important work has followed. It should be noted that he was also aided by the newly introduced adaptation of Ehrlich's diazo test for bilirubin (van den Bergh & Snapper 1913). Although this reaction was of great help it did not solve all the problems as we can see from van den Bergh's own classification into mechanical and dynamic jaundice (1918) which was never widely adopted.

While McNee's classification has survived substantially unchanged, several minor modifications of nomenclature have been proposed, as shown in Table 1. Of these, the terminology of Rich virtually abandons the hard-won distinction between hepatic and extrahepatic jaundice, and has not been popular in this country. Those of With and Lichtman are merely alterations in nomenclature, but the latter's terminology does seem to represent a real improvement since his terms are short and unequivocal. I have suggested elsewhere the substitution of 'post-hepatic' for 'extrahepatic' as harmonizing better with 'pre-hepatic' (Maclagan 1957).

The van den Bergh Reaction

Following the work described above, an intensive biochemical attack on the basis of the van den Bergh reaction commenced and is still going on. The gross chemical structure of bilirubin had apparently been settled by Kuster (1909) so that the finding of more than one type of reaction required some explanation. Van den Bergh himself recognized only two types of reaction in aqueous media, namely the delayed and the immediate. Feigl & Querner (1919) added a description of the 'biphasic' reaction which was also adopted by McNee in 1923. These three types of reaction were originally thought to be typical of prehepatic, post-hepatic and hepatic jaundice respectively, but the distinction between the last two was always somewhat dubious. This difficulty was pointed out particularly by Harrison (1930), and there has been, over the period, a gradual disillusionment as to the value of the test in distinguishing hepatic from post-hepatic jaundice (Gray 1947). During the period 1918–1953 considerable difference of opinion arose as to whether van den Bergh had been correct in supposing that his two types of reaction were due to two different pigments, or whether a single pigment differently combined was responsible for all the phenomena observed. The early workers were particularly impressed with the difference in chloroform solubility of the pigment in different types of jaundiced sera (Grunenberg 1923, Newman 1928, Heilbrun & Hubbard 1940). In agreement with this, Griffiths (1932) and Fowweather in the same year claimed to have shown that the main pigment of bile was distinct from bilirubin. However, later workers sought to explain the different types of reaction mainly on the basis of different modes of combination with protein or by the presence of activators. This field was reviewed by Gray in 1953. It was, therefore, a very pleasant surprise when Cole, Lathe & Billing (1954) announced the unequivocal isolation of *three* different but related pigments from jaundiced sera; later identified as free bilirubin and its mono- and di-glucuronides (Billing & Lathe 1956, Schmid 1956). This work appears to reconcile all the previous observations on the van den Bergh reaction, and has added a most interesting chapter to the biochemistry of bile pigments. It now appears that sera from post-hepatic jaundice may contain more of the di-glucuronide than sera from hepatic jaundice, while in the case of pre-hepatic jaundice the pigment is mainly in the free state. It remains to be seen whether the statistical differences between the first two of these groups will be sufficient to make the test useful in diagnosis as suggested by a recent report (Hoffman *et al.* 1960). The technique is, unfortunately, difficult to make strictly quantitative and not very suitable for routine application (Billing 1960).

Anomalous Types of Hepatic Jaundice

An important result of this work has been the provision of a satisfactory explanation for a number of examples of jaundice which had previously been little understood. These are the types of constitutional hyperbilirubinæmia, mild examples of which were described by Gilbert & Lereboullet in 1901, and more severe examples by Crigler & Najjar in 1952. The mild examples are compatible with good health, but the more severe varieties may cause death in infancy from kernicterus. These are now recognized as being due to partial

or complete failure in the conjugation of bilirubin with glucuronic acid by the liver. The enzyme system responsible for this conjugation has been defined, and has been shown to be diminished in patients with these complaints. A similar condition exists in the neonatal liver and is an important contributory cause of neonatal jaundice (*see* reviews by Billing & Lathe 1958, Arias 1960).

A further anomalous type of hepatic jaundice is the variety which has been called 'cholangiolytic' or 'cholestatic' (Watson & Hoffbauer 1946, Sherlock 1958, Hoffbauer Symposium 1958). This may occur after relief of biliary obstruction, after infective hepatitis, or after certain drugs such as chlorpromazine or methyl testosterone. The jaundice is thought to be due to an abnormal permeability of the bile capillaries. The functional changes are very similar to those seen in post-hepatic jaundice, so that the usual tests may be unhelpful in diagnosis which therefore has to be made mainly on clinical grounds.

Infective and Hæmolytic Diseases Causing Jaundice

There is little opportunity here to consider the parallel advances in bacteriology and hæmatology which have made such important contributions to the study of jaundice. We can only recall very briefly that work during the last 60 years has established beyond doubt the true nature of yellow fever (1900–1911), Weil's disease (1914), infective hepatitis (1939–1944), homologous serum jaundice (1937–1944) and neonatal jaundice (1941–1954). The comparatively recent clarification of the last three conditions is somewhat surprising and merits further consideration.

'Icterus gravis neonatorum' was a complete puzzle to early workers, and little fundamental advance in this subject was possible until the discovery of the rhesus blood groups by Landsteiner & Wiener in 1940. The possible occurrence of maternal-fœtal incompatibility, which was under consideration at that time, was rapidly correlated with the Rh system by Levine *et al.* in 1941 and these workers clearly established the relationship between rhesus incompatibility and severe neonatal jaundice. This was not, however, the whole story and the important contribution of hepatic immaturity had to wait until the discovery of bilirubin conjugation described above (1953–4).

In 1957 Lathe & Walker produced the final proof of the importance of impaired conjugation by showing that the newborn liver was extremely deficient in glucuronyl transferase, thus explaining at once the presence of 'physiological' neonatal jaundice, the increased incidence of this in premature infants, and the unusual severity of the hæmolytic jaundice in cases of erythroblastosis fœtalis. In all these cases the absence of jaundice at birth is, of course, due to the placental removal of bile pigment.

The story of infective hepatitis makes another fascinating chapter in medical history which could easily be expanded into a volume. Although epidemics of infective jaundice had been recognized from earliest times they were little understood, and for many years there was some confusion with Weil's disease. Later such epidemics were for a long period ascribed to gastroduodenal catarrh with biliary obstruction by mucus (Virchow 1865). The situation was ably reviewed by Cockayne in 1912 who concluded that the disease was due to an infective agent of unknown nature. In 1920 Eppinger reported biopsies on 3 cases who had died from trauma and described 'an acute yellow atrophy in miniature'. However, the notion of 'catarrhal jaundice' died hard and was not really abandoned until the introduction of the liver puncture technique by Iverson and Roholm in 1939. This established clearly the nature of the liver condition as an acute hepatic necrosis, and these results were soon confirmed by Dible *et al.* in 1943, and extended by them to include homologous serum jaundice as an identical pathological condition. This disease had only just become recognized as a sequel to blood transfusion, intravenous injection and even blood collection by venepuncture, and the infective nature of both types of infective jaundice was finally proved by MacCallum & Bradley and MacCallum & Bauer (1944) who transmitted them successfully to human volunteers. Following this work the institution of proper syringe sterilization in syphilis clinics produced a dramatic fall in the incidence of what had previously been called 'arsenical jaundice'.

Although the hepatic lesions of infective hepatitis and of serum jaundice appear to be identical, they are due to different viruses and differ in their incubation periods (longer in serum jaundice) and in the incidence of positive flocculation tests which is much higher in infective hepatitis (Maclagan 1944). Possibly both these differences may be due to the fact that in serum hepatitis virus and antibody are administered simultaneously. The very late recognition of these two important infective diseases still appears surprising and was due in part to the lack of a susceptible animal to which they could be transmitted, a limitation which continues to hamper progress in the virology of these conditions. It is interesting to compare this situation with other examples of infective jaundice such as yellow fever and Weil's disease, the much earlier recognition of which was, perhaps, dependent on the more dramatic symptomatology, the shorter incubation periods, the

presence of insect vectors and the strong geographical or occupational associations.

Differential Diagnosis

From the laboratory point of view it is usually easy to distinguish pre-hepatic jaundice from the other varieties, but much work has been expended upon devising tests which might be of help in distinguishing the hepatic from post-hepatic jaundice. In this connexion I have recently developed a simple statistical procedure for testing the efficiency of various tests for this purpose which consists of the calculation of a 'Diagnostic Efficiency Index' (Maclagan 1960). The use of this Index is illustrated by application to personal data on the thymol flocculation test as shown in Table 2. The procedure is to calculate the percentage of cases having positive and negative results in hepatic and post-hepatic jaundice respectively. Cases with positive results in hepatitis and with negative results in post-hepatic jaundice are counted as showing 'correct' results, and the average of these two figures gives the Diagnostic Efficiency Index. This represents mathematically the probability of arriving at a correct diagnosis in a case drawn at random from equal groups of the two conditions if the thymol flocculation test is used as the sole criterion of diagnosis. It will be seen that the test is more uniformly negative in post-hepatic jaundice than it is positive in hepatic jaundice: paradoxically, therefore, positive results are more significant in diagnosis than negative ones. This treatment ignores various considerations such as the time factor and is merely intended as a means of comparing one test with another. The application of this procedure to a number of the more popular tests has shown that while many achieve figures of above 80% for the Diagnostic Efficiency Index, very few reach 90%. Among the latter are the thymol flocculation-alkaline phosphatase combination which scores 90% (Maclagan 1947), the Jirgl flocculation test at 91% (Jirgl 1957, Daikos *et al.* 1959), the prothrombin response to vitamin K (96%, Stein 1944) and the serum bile-acid ratio of Carey (1958) which gives a figure of 90%. The first of these has been widely used and is possibly as good as any of the others, the prothrombin response to vitamin K is only applicable in those cases where the prothrombin is initially low (about 25%) and the Jirgl flocculation test and the bile-acid ratio are both newcomers to the field, and have not been very thoroughly explored. Undoubtedly more work on these tests would be of interest at the present time.

Table 2

Diagnostic Efficiency Index for the Thymol Flocculation Test

Calculated from data on 200 cases (Maclagan 1947)

	Hepatic	*Post-hepatic*
% above 1+	71	0
% 1+ or negative	29	100

$$\text{Diagnostic Efficiency Index} = \frac{71+100}{2} = 85\% = \text{Probability of correct diagnosis}$$

Conclusion

Have we then any final conclusion about the nature of jaundice, or any modification to suggest in the existing classification? One important addition to the list which we must, indeed, take into account is the case of conjugation failure discussed above, and Table 3 suggests how this can be fitted into the previously existing picture. A somewhat similar classification has recently been proposed by Nosslin (1960). Table 3 preserves the three main divisions of jaundice, but recognizes two very different types of hepatic jaundice, one due to a selective failure of conjugation, the other to a generalized liver damage where the jaundice is presumably due to partial secretion of conjugated bilirubin followed by reabsorption from the bile capillaries. Incidentally the nature of this reabsorption is still not entirely settled, and it may take place either directly into the hepatic venous circulation or into lymphatic channels. The mechanisms involved have been carefully investigated by Weinbren (1952). There is little justification for speaking of '*intra-hepatic obstruction*' in this condition since there is no clear

Table 3

Types of Jaundice

Name	*Cause*	*Serum bilirubin*	*Urine bilirubin*	*Stool pigment*	*Other liver functions*
Pre-hepatic	Over-production	Free	Absent	Increased	Normal
Hepatic	(1) Conjugation failure	Free	Absent	Normal or reduced	Normal
	(2) Partial excretion + reabsorption	Conjugated	Present	Reduced	Impaired
Post-hepatic	Excretion + reabsorption	Conjugated	Present	Reduced	Normal

evidence that mechanical obstruction is present, the more likely possibility being one of increased permeability of the bile capillaries. This terminology appears to be a reversion to the much older ideas which were current around 1900, and one feels that the term is a source of confusion at the present time.

It will be seen from Table 3 that the pigmentary results of hepatic jaundice (1) are very similar to those of pre-hepatic or over-production jaundice; the fæcal pigment excretion is, however, quite different and there is no collateral evidence of hæmolysis in the hepatic type. Similarly the pigmentary results of hepatic jaundice (2) are, for all practical purposes, identical with those of post-hepatic jaundice, and the best chance of distinguishing these two varieties is to employ tests such as the enzyme and flocculation tests which do not depend directly upon biliary excretion.

Problems for the Future

What advances may we expect in this field in the future? Prophecy is always dangerous, but I would suggest that we are never likely to find any test which will be completely infallible in the diagnosis of jaundice, since the results must always be interpreted with due regard to the clinical picture. We may certainly hope that further experimental work may show the exact mechanism of jaundice in hepatitis and in biliary obstruction. The discovery of further anomalous types of hepatic jaundice involving enzyme or other defects is obviously a possibility and much remains to be done in the field of virology in relation to infective hepatitis.

In conclusion, it may well be asked whether it has been worth while to try to trace the history of a single symptom in the way which I have done here, but I hope that I have been able to show that attempts to explain the nature of jaundice have involved speculation and research over a wide spectrum of subjects including folk-lore, medicine, surgery, pathology and chemistry and that these attempts have in the end added much to our knowledge of disease in general.

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Section of Neurology

President W H McMenemey MD FRCP

Meeting October 6 1960

President's Address

Immunity Mechanisms in Neurological Disease

by W H McMenemey MD FRCP (*London*)

During the last decade progress in immunology has been spectacular and much of it is relevant to clinical neurology. Of special interest is the new biological approach to immunity which, despite the fact that hypothesis and speculation have outpaced scientific confirmation, poses important problems. The key to the clinical study of immunity is in the globulins, with which and with their significance my Address is principally concerned, drawing attention in particular to the important help afforded to neurologists by electrophoresis.

The Protein Pattern in Cerebrospinal Fluid as revealed by Electrophoresis; and the Role of the Choroid Plexus in the Formation of the Fluid

When Tiselius (1930) made use of free electrophoresis in a study of plasma proteins defining albumin, fibrinogen and three globulins α, β and γ, he set up a landmark in the history of protein analysis. Others after him made use of a variety of techniques. Although paper, as a supporting medium – which was the first to reveal two distinct α fractions – has been largely superseded by agar, cellulose acetate and starch, much of the early work remains valid. In 1955 Williams & Grabar introduced the two-stage technique of immunoelectrophoresis. In essence this consists of the demonstration by suitable staining techniques of specifically fixed antibodies precipitated during a process of diffusion after electrophoresis. The point of combination – or the zone of equivalency – is revealed in the form of a slightly elongated arc.

The first to adapt electrophoresis to cerebrospinal fluid (C.S.F.) appears to have been Hesselvik (1939). In an attempt to compare protein patterns of various body fluids with those of serum he employed free electrophoresis. In general he noted good agreement but whilst in serum he found four protein fractions, in the fluids there were but three and sometimes only two. In two cerebrospinal fluids, both from paretics, he identified only one globulin which he claimed to be the γ fraction.

Kabat *et al.* (1942) went further and established three facts: (1) That the changes in the C.S.F., though seldom marked, reflect those in the serum, (2) that the γ-globulin is responsible for a first zone Lange curve (as indeed had for long been assumed), and (3) that in neurosyphilis γ-globulin occurs in the fluid over and above the level one would expect having regard to that in the serum. In 1950 Kabat *et al.*, using anti-γ-globulin serum in quantitative studies, reported the presence in C.S.F. of excess γ-globulin in diseases other than neurosyphilis and multiple sclerosis including postvaccinal encephalitis, cerebral carcinomatosis, polyarteritis nodosa and Raynaud's disease.

Paper strip electrophoresis was adapted to C.S.F. by Schneider & Wallenius (1951) and in the same year they presented their findings to the First International Congress of Clinical Pathology in London. Because of the small quantities of protein normally present in fluid as compared with serum there have been many difficulties to overcome including obviation of the possibility of denaturation during the process of concentration. However, progress has been swift and paper has again been largely abandoned in favour of other supporting media. In 1955 immunoelectrophoresis was successfully adapted to cerebrospinal fluid by Gavrilescu *et al.*

Formerly it was believed that the choroid plexus acted as a simple dialysing membrane between blood and C.S.F. and that the protein fractions were in the same relative proportions but Greenberg *et al.* (1943), making use of radioactive isotopes, noted a hindrance to the free passage of ions and a deviation from the Donnan Law of distribution which indicated a secretory activity on the part of the choroid plexus. Kabat *et al.* (1950) drew attention to the fact that the heavier molecules of globulin were not present in the fluid in the same ratio as in blood, since when

many have noted differences in the proportions of various protein fractions (Fisk *et al.* 1951, Hoch & Chanutin 1952, Gries *et al.* 1953, Field 1954, Gavrilescu *et al.* 1955, Uzman & Bering 1956, Mumenthaler & Märki 1957): in fact, one component found electrophoretically in cerebrospinal fluid, the τ-fraction of Bücher *et al.* (1952) – often called β_2 – appears not to have its counterpart in serum. The pre-albumin fraction (Kabat *et al.* 1942, Scheid & Scheid 1944, Fisk *et al.* 1951, Hoch & Chanutin 1952, Bücher *et al.* 1952, Gavrilescu *et al.* 1955, Booij 1956) so readily identified in C.S.F. has been shown to be present in serum when agar is employed as a supporting medium (Grabar & Williams 1953). Frick & Scheid-Seydel (1958) concluded from their studies with γ-globulin tagged with ^{131}I that γ-globulin traverses the choroid plexus more slowly than the albumin, a dynamic equilibrium between serum and C.S.F. being achieved in about one hundred hours. In diseases commonly associated with a first zone Lange curve they were able to show that while part of the γ-globulin came from the serum there was present another part of that globulin which did not come from the serum and which could exceed 90% of the total. It became therefore an established fact that γ-globulin could find its way into the C.S.F. otherwise than through the choroid plexus of the lateral ventricles.

Transferred Patterns in the Cerebrospinal Fluid in Somatic Disease and the Value of Serum Patterns in the Investigation of Neurological Disease

As an example of a condition mirroring in the C.S.F. the protein pattern in the serum we may quote myeloma. In this disease the total protein content of the C.S.F. may be increased in the absence of a block or of any neurological lesion and in the serum the rise is in the globulin. The following cases illustrate the range of globulins which may be detected in the serum and C.S.F.

Case 1 A 55-year-old spinster, employed as a clerk, developed a sudden pain in the small of the back with weakness of both legs. From that moment she remained in bed and although at first a diagnosis of hysteria was entertained, it was soon realized that her early paraplegia was organic in character. She was later admitted under the care of Dr R A Henson and a diagnosis of multiple myelomatosis was made with collapse of D.11, X-rays having revealed marked osteoporosis of both dorsal and lumbar spine with deposits also in the skull, cervical spine and ribs. There was no proteinuria. The E.S.R. (Westergren) was 91 mm in one hour and later 122 and the serum proteins 13·9g%.

The serum protein pattern (paper) showed a marked increase in the γ-globulin and moderate increase in α_2 and decrease in the albumin fraction. The C.S.F. was colourless with a protein of only 34 mg%, and a Lange curve of 111000; however, a protein pattern

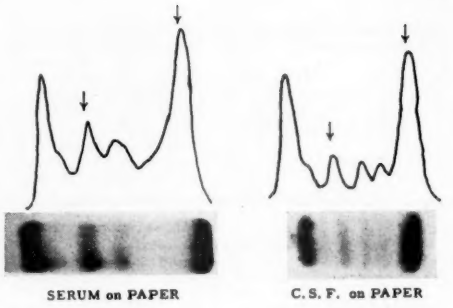

Fig 1

(paper) was obtained which faithfully mirrors the serum (Fig 1).

At operation quantities of an extradural tumour were removed which was histologically a myeloma.

Serre *et al.* (1958) have provided proof of the ability of the tumour cells to produce this globulin. It, however, is not the only fraction–although it is the commonest – to be met with in myeloma.

Case 2 A 56-year-old welfare officer Dr N G Hulbert's patient, gave a history of progressive numbness and of weakness of the legs over a period of three months with eventual loss of sphincter control. One year previously he had been treated in India for a macrocytic anæmia with vitamin B_{12} and shortly afterwards had what was called 'pleurisy'. He was found to have a compression paraplegia due to collapse of D.3. The blood count was within normal limits but the sternal marrow contained 4·5% plasma cells and 1·75% cells in mitosis and the E.S.R. (Westergren) was 55.

The serum (on paper) shows a considerable increase in the β and rather less in the α_2. In the C.S.F. (cellulose acetate) the profile is reproduced, the principal increase being in the β (Fig 2). Having collapsed just before operation he was instead treated with deep X-ray, since when he has improved and remains with a mild paraplegia and control of his sphincters.

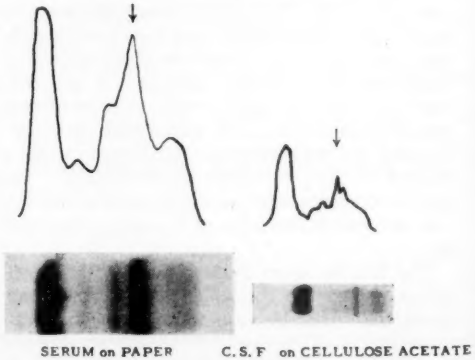

Fig 2

In this case therefore there is a strong presumptive diagnosis of myeloma with a production of a globulin which appears in excess in the β-fraction. Gergely & Szinay (1960) demonstrated immunoelectrophoretically in 2 cases of myeloma that the protein in tumour homogenate extract was identical with that they had found in excess within the β range of the serum.

Case 3 A 57-year-old engineer, while going downstairs, experienced a sudden pain in the small of the back which persisted and later radiated down the front of both thighs. Within six weeks the pain was accompanied by numbness of the toes and a week later, after watching television, he found himself unable to rise from his chair. He had a partial collapse of D.11 with extradural compression, the lumbar fluid being yellow with 2 cells and a protein content of 500 mg%. The blood count was normal but the E.S.R. (Westergren) was 70 mm. There was no proteinuria.

The serum electrophoresis (paper) showed a marked increase of the α_1 and the α_2 and between β and a low γ was a globulin interpreted as a serum Bence-Jones fraction (Fig 3). The C.S.F. (on paper) mirrored this

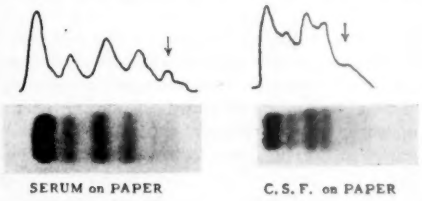

Fig 3

finding but it has to be remembered that in this case serum has almost certainly gained access to the fluid probably through venous congestion although an added local accession of protein is not impossible.

Mr Valentine Logue relieved the compression and a typical myeloma was found. No other tumours were identified and the only other disease in this man's history was that of recurrent herpes as a child.

This then is an instance of myeloma, the cells of which appear to have produced globulins which are in the position of the usual α_1 and α_2 and also an abnormal one which lies between the β and γ. The identity of the finding in tumour homogenate extracts with the α fractions in the serum has not yet, so far as we know, been established.

These three examples illustrate the facts that the myeloma cells produce globulin in quantity, that such globulin may correspond to one of the recognized fractions or it may have its own rate of migration, and that the tumour cells can probably produce globulin of more than one rate of migration. They show also that if the choroid plexus is functioning in the normal way an abnormal serum pattern is mirrored in the C.S.F. and if reliance is placed only on the total protein and Lange curve – at any rate in cases of myeloma – significant abnormalities in the protein fractions may be overlooked.

Many systemic diseases associated with an increase in globulin will show a transferred pattern. In cirrhosis hepatis, for instance, one finds in the cerebrospinal fluid the same striking increase in the γ fraction that is present in the serum. One may expect it also in other diseases which are associated with an increase in this fraction and yet are uncomplicated by extension of the pathology within the brain as, for instance, sarcoidosis and many bacterial, fungal and parasitic infections.

Antibody globulin is to be found in the γ fraction and to a lesser extent in the β fraction. However, not all of the γ fraction, either in blood or C.S.F., is antibody globulin and the same holds for the β fractions: an increase in either fraction, however, but especially the γ, is suggestive of antibody formation.

An increase in the α-globulin is commonly associated with tissue destruction and inflammation, and it may be transferred from the serum to the C.S.F. It is to be expected in the presence of widespread malignant disease, as the following case illustrates.

Case 4 A 67-year-old retired house decorator suffered initially from giddiness and unsteadiness of gait but when admitted under the care of Dr Redvers Ironside with pain in the back was found to have ptosis rather more on the left than on the right, a left pupil somewhat larger than its fellow, weakness and wasting of digital muscle groups, absent knee and ankle jerks, a blood pressure of 210/110 and ascites. Two years previously a kidney had been removed on account of a papilloma of the renal pelvis. He had a secondary anæmia, an E.S.R. (Westergren) of 16, albuminuria and Bence-Jones proteosuria, and a lumbar C.S.F. which gave a protein of 35 mg% and a negative Lange curve. Plasma cells, including binucleate forms, amounted to 2·8% in the sternal marrow count. The protein patterns in both serum and C.S.F. (on paper) showed a marked increase of the α_2 and in the C.S.F. of the α_1 also (Fig 4).

At necropsy he was found to have widespread intraperitoneal deposits of renal carcinoma. There were none in his nervous system but he had a moderate

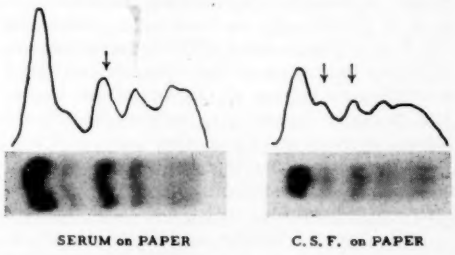

Fig 4

degree of cerebral arteriosclerosis, with ventricular dilatation, a few small areas of encephalomalacia and occasional slit hæmorrhage.

The serum protein patterns are partly mirrored in the fluid but it will be noticed that the α-globulins are correspondingly higher in the C.S.F. perhaps on account of the encephalomalacia: the albumin is correspondingly reduced.

Any systemic disease therefore which is associated with an increase in the circulating α, β or γ globulins can be expected to mirror the change in the C.S.F. We have had no opportunity to compare serum and fluid patterns in agammaglobulinæmia, but would expect the absence of γ-globulin in the serum to be reflected in the fluid. We have, however, examples of abnormally low γ levels transferred to the C.S.F.

While we advocate comparing whenever possible the patterns of serum with those of C.S.F., we have on many occasions found a serum pattern helpful in diagnosis in cases in which C.S.F. has not been available for study.

Autochthonous Patterns in the Cerebrospinal Fluid

Autochthonous protein patterns in the C.S.F. may be expected in diseases which are wholly or principally confined to the central nervous system, as for instance multiple sclerosis and encephalitis.

Multiple sclerosis: A feature of multiple sclerosis is that the C.S.F. electrophoretic pattern differs fundamentally from that in the serum. However, in common with others (Volk *et al.* 1954) we have found that there are changes in the serum. The interpretation of these patterns requires caution because, given standard conditions of collection and of technique, one has still to consider such factors as past illnesses, intercurrent infections – some of them possibly subclinical – and secondary infections. Nevertheless, there does seem to emerge a certain serum pattern during the course of the disease which may be summarized as an early increase in the β followed by a similar one in the α_2 and a borderline increase in the γ-globulin.

In the C.S.F. the increase is in the γ only and it is less marked than in leucoencephalitis and its peak is shorter and its base wider, differences which according to Booij (1959) must be accounted for by the nature of the γ-globulins involved. According to Yahr *et al.* (1954) multiple attacks and multiple lesions are associated with the biggest increases in the γ fraction.

Of interest are the changes which follow the intrathecal administration of P.P.D. Field, as early as 1954, working with paper strips, referred in such cases to finding an increase in the γ-globulin fraction in the C.S.F. We quote a typical case from a series shortly to be published.

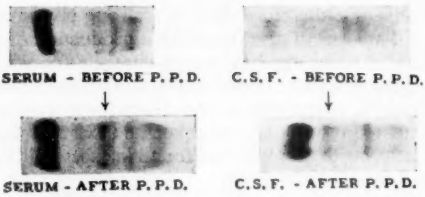

Fig 5 *On Cellulose Acetate*

Case 5 An electrician noticed a transient weakness of the right leg at the age of 25: some months later both legs became affected and he complained of diplopia. After a period of observation under the care of Dr R E Kelly it became clear that his disease was advancing, so he was treated at St Thomas's Hospital with intrathecal P.P.D. The protein studies shown in Fig 5 were made one week after the second injection which was not succeeded, as was the first, by a febrile reaction.

It will be noticed (*a*) that the pattern is autochthonous and (*b*) that the tuberculin provoked in the C.S.F. a marked increase in the α_1 whereas in the serum the increase was most marked in the α_2.

Encephalitis: A first zone Lange curve has often been reported in subacute and chronic forms of encephalitis including Dawson's type, the identity of which with the subacute sclerosing leucoencephalitis of van Bogaert most authors seem prepared to accept. The electrophoretic patterns in the C.S.F. are similar, the γ-globulin being constantly raised. Booij (1959) reports an increase in the γ-globulin even though the total protein may be little raised – if indeed at all – and the α_2 and the β fractions may actually be decreased. Similar findings have been reported by van Wymeersh *et al.* (1957). In Pette-Doring form of subacute encephalitis, Bauer (1959) has reported similar findings. Vymazal *et al.* (1959) have also commented on an increase in the α_2. The evidence of electrophoresis therefore is in favour of the identity of these forms of subacute encephalitis. Of interest is the fact that the γ fraction often falls shortly before death (Bauer 1959).

In neurological complications of systemic diseases associated with abnormal serum patterns, general paralysis for instance, the recognition of an autochthonous pattern in the C.S.F. may be difficult because of the accession of serum globulin either by transference through the choroid plexus or through a diseased or functionally relaxed vascular barrier within the brain.

The Possibility of 'Overflow' Patterns in the Serum from Brain Disease

As it appears certain that a somatic globulin is able to reach the C.S.F. by reason of the secretory activity of the choroid plexus it might be expected that any globulin manufactured within the central

nervous system and finding its way into the C.S.F. could eventually reach the circulation either by absorption through the arachnoidal villi or perhaps by direct transfer into the cerebral vessels through the intermediary of perivascular histiocytes. One would have to reckon with a considerable factor of dilution and would expect to detect a reflection in the serum only when the increase in the particular fraction in the fluid is considerable.

In certain cases of subarachnoid hæmorrhage shortly after the incident an increase in the α-globulins has been noted in the serum which may have been related to the immediate pathology but the possible effect of arteriography, and in particular the extravasation of blood into the tissues of the neck, has to be taken into account.

Case 6 A 56-year-old woman, Mr Logue's patient, had three intracranial aneurysms revealed by arteriography on the third and seventh days after a hæmorrhage. A month later further bleeding occurred; the serum pattern obtained on the following day shows that the α_2 is increased and the γ is low (Fig 6).

Case 7 A 50-year-old woman was admitted on the day of a hæmorrhage and a protein pattern showing an increase in the α_2 was obtained on the following day (Fig 6). Twenty-one months previously Mr Logue had ligated an aneurysm on the right posterior communicating artery.

Case 8 A female, aged 49, was admitted on the fourth day of her illness under the care of Mr Logue and a basilar aneurysm was demonstrated. The serum on the fifth day of her illness shows an increase in the α_2 (Fig 6).

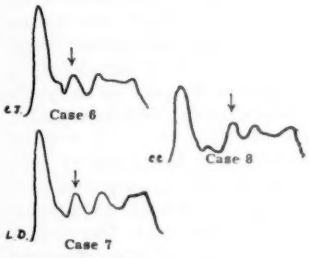

Fig 6 *On paper*

The effective area of the subarachnoid mesenchymal membrane concerned in the degradation of hæmoglobin and its subsequent phagocytosis is extensive and the cellular response at times may be marked. Nevertheless the possibility of α_2-globulin being due to tissue damage in the neck or being produced somatically to aid the reparative process seems more likely than an overflow pattern from the C.S.F. to the serum.

We can conclude: (1) That C.S.F. electrophoresis is both more accurate and more revealing than the Lange gold curve, which it can well replace as a standard procedure. (2) That C.S.F. electrophoresis should be carried out in conjunction with serum electrophoresis for the assessment of local globulin production within the central nervous system. (3) That the serum findings are reflected in the C.S.F. but that local production of globulin within the central nervous system cannot be expected to show in the serum because of the considerable degree of dilution involved.

The value of electrophoresis is not confined to diagnosis. Vazquez de Negrotto *et al.* (1957) have shown its prognostic value in tuberculous meningitis, and in particular the favourable outcome in those treated cases when the α-fractions in the fluid fall and the γ rises.

The Significance and Constancy of Individual Electrophoretic Peaks in the Serum and Cerebrospinal Fluid in terms of Specific Molecular Weight, with Special Reference to the γ-fraction

Having regard to the known complexity of protein one might expect to find electrophoretically in both blood and C.S.F. an almost infinite variety of fractions. However, from electrophoretic data it is clear that while albumin and fibrinogen (this latter seen in plasma but not in serum) are reasonably homogeneous – the high sharp peak corresponding to a migration of protein ions the majority of which have the same net charge and weight – globulin consists of a number of types of ions. They may be classed roughly into the three groups of Tiselius but include species of varying mobilities within any one group.

Later workers have been able to show that these three globulins may be resolved into further components and their separation may be accomplished by changing the supporting medium, the buffer, the pH and the current. Using an ultramicroelectrophoretic technique on agar Wieme (1958) found 4 γ subfractions in the serum while Booij (1959) noted 4 in the C.S.F. of which subfractions 1, 2 and 3 were raised in multiple sclerosis while in leucoencephalitis – using this term generically – it was the 2nd, 3rd and especially the 4th components which were prominent. Lowenthal *et al.* (1960) with the same technique noted six separate peaks. However, with some ultramicroelectrophoretic techniques in C.S.F. it is too early to exclude the possibility of artifactual formation of these presumed subfractions.

With Kohn's cellulose acetate technique (1958) one γ-globulin both in serum and C.S.F. appears to be the rule so that when one does find a second peak one assumes that it is pathological. We have

noted a slow-moving component in the C.S.F. of the second of two siblings[1] with symptoms and histological findings pointing to widespread progressive disease of the cerebral cortex and of the white matter.

For some time my colleague, Mrs Gavrilescu, has been interested in an abnormal protein found in the C.S.F. by immunoelectrophoresis in some cases of multiple sclerosis. It is revealed as a long, straight precipitation line running almost parallel with the γ and crossing into the β group: it is a little more elongated, otherwise similar to β_2M macroglobulin.

In the serum of a case of Guillain-Barré's disease in a man aged 62 an extra peak was noted with a variably increased protein of a β_2 mobility between the β- and γ- globulins on paper, agar, and cellulose acetate electrophoresis. This case, under the care of Dr S Nevin, has been followed for four years and the extra β fraction was at one time the predominant globulin. The lipoproteins have been normal. Professor P Grabar kindly confirmed our findings immunoelectrophoretically and no reaction was obtained with serum 1299 (Pasteur) macroglobulin, thereby excluding the possibility of macroglobulinæmia.

The isolation of individual protein fractions such as the three we have mentioned and their further study by chemical and physical means might well be rewarding.

Grabar (1954) has marshalled the arguments in favour of the γ-globulin constituting a heterogeneous group. We have already seen that it is possible to obtain different subfractions electrophoretically, and it is known that these subfractions have differing molecular weights, isoelectric points and solubilities. Most important of all is the fact that in the γ group there are antibodies with very different specificities. On the other hand immunoelectrophoresis shows that, in spite of the differences in the migration rates, γ-globulins can act with the same antibodies, thus indicating that antigenically they are identical or very close. The uniformity of the γ-globulins is further indicated by the constancy of the analytical findings when they are broken down to amino acids.

The Roles of the Plasma Cell and the Lymphocyte and the Source of the Antibody Globulins in the Cerebrospinal Fluid

It is generally agreed that the function of the plasma cell is to produce some, if not all, of the antibody globulins (Makinodau *et al.* 1954, Marshall 1956). Myeloma tumour homogenates have yielded globulin electrophoretically identical with that found in excess in the serum in both the γ and β ranges and possibly in the α range also. Moreover, Nossal (1958) has succeeded in isolating globulin from the cytoplasm of individual plasma cells. Finally, plasma cells are not found in those with agammaglobulinæmia. The absence of plasma cell proliferation, noted by Fagraeus (1948) during recovery from severe plasma depletion, is usually claimed as evidence for the view that plasma cells are not concerned with the secretion of normal but only of antibody globulin.

Concerning the lymphocyte which is so conspicuous in chronic inflammatory states, there is no general agreement as to its role although there is no dissent from the classical view that it is formed in lymphoid tissue, circulates in the blood stream and plays a part in the reparative stage of inflammation. Neuropathologists are agreed that the presence of lymphocytes around a blood vessel does not necessarily imply an infection. They are mobile cells and, as Pulvertaft (1959) reminds us, are unique in being able to penetrate a cell membrane and circulate freely within the confines of its cytoplasm. Burnet (1959) suggests the possibility of varied functional potentialities for this mesenchymal cell and metamorphosis might be in the direction of the plasma cell. This is an old idea with, however, little evidence yet to support it. Lymphocytes might be credited with the ability to fetch and carry antibodies were it not for the facts that their cytoplasm seems unsuited for the purpose and that plasma cells are so commonly found in inflammatory states of the brain that delivery of the antibody to the right spot seems to be already guaranteed. More likely is the alternative view that these cells supply nucleoproteins wherever they are wanted. When we see them nuzzling the cells of the advancing edge of a carcinoma they are perhaps serving a physiological purpose although we may regard it as a misguided one.

In the Haurowitz-Pauling hypothesis of antibody production the antigen is visualized as a template inside the plasma cell against which the antibody globulin is manufactured. The current Burnet theory of clonal selection allows a greater degree of specificity on the part of the antigen and of the antibody-forming cell, for it is envisaged that a specific antibody is initiated by a certain genetically-determined group (or clone) of cells when it is stimulated by the appropriate antigen. In endeavouring to apply this theory to the central nervous system one looks for a local source of mesenchyma and apart from the blood cells finds but four possibilities which can all be discounted: (1) The lymphoid tissue of the nasopharynx, (2) certain cells of the pineal organ (altogether too few to be immunologically competent), (3) the

[1]These cases under the title of 'Familial poliodysplasia with leucodystrophy' were presented to the Section of Pathology on October 20, 1959, by Dr P H Buxton who will shortly publish them.

Hortega cells which, while capable of phagocytosing an antigen and perhaps transporting it to the appropriate clone, have shown no evidence of ability to produce antibodies, and (4) the arachnoidal cells, for which there is again no evidence of their ability to produce globulin. One concludes, therefore, that antibodies required by the brain are imported by circulating plasma cells and that the manufacturing clones must be sought elsewhere than within the confines of the skull. The autochthonous γ-globulins found in the C.S.F. in cases of encephalitis are there, one presumes, because they have been released by blood-borne plasma cells which have penetrated the walls of cerebral blood vessels. The same could happen in multiple sclerosis for, especially in the more acute lesions, plasma cells are found. On histological grounds one finds it difficult to recall a disease with an excess of γ-globulin in the fluid which cannot have been imported by the blood stream through the intermediary of plasma cells. On the other hand it is premature to exclude the possibility that some γ-globulin in the C.S.F. is due to tissue destruction.

The β-globulins and the Lipoproteins

On paper electrophoresis the β fraction includes not only some of the antibody globulins but also the lipoproteins. An increase in this fraction therefore has conveyed a suggestion of the ageing process for it has been reported in cerebral atrophies (Bauer 1953), in Creutzfeldt-Jakob's disease (Sluga-Gasser 1959) and in presenile, senile and post-traumatic dementia (de Rissio *et al.* 1957). However, with the cellulose acetate technique, as with agar, the lipoproteins are associated with the α_2 and not with the β fraction. Moreover, with paper electrophoresis the decrease in the serum albumin relative to the globulin and the actual increase in the β-globulins due to the lipoproteins seem not to be transferred to the C.S.F. For these reasons we are interested in the raised β-fraction in the C.S.F. in the following case of presenile dementia.

Case 9 A 53-year-old woman clerk, who had shown symptoms of mental deterioration progressing over a period of four years and had been reduced to cleaning bottles until she took to her bed in a depressed state, was admitted under the care of Dr Nevin for investigation. The only history of previous disease was of a tuberculous abscess of the lung fifteen years earlier. Electrophoresis (Fig 7) showed that a marked increase in the serum β-globulin (on paper) was reflected in the β fraction in the C.S.F. (on cellulose acetate). Cerebral biopsy confirmed the clinical diagnosis of Alzheimer's disease.

The three sera in Fig 8 are from cases of chorea (Cases 10, 11 and 12) and they all show with paper electrophoresis a rather characteristic pattern with a raised β and a peculiar plateau-like γ.

Case 10 The first is from a 53-year-old man, Dr Nevin's patient, whose abnormal movements had apparently begun within the year and shortly after a fall at work. Clinically he resembled Huntington's chorea. Both the patient and his wife were unreliable witnesses and he had lost touch with all members of his own family for seventeen years. There was a history, however, of his mother having died in a mental hospital when he was aged 30.

Case 11 The second is from a 48-year-old man well known in several hospitals as a case of Huntington's chorea. The family history is inconclusive but his father and a brother died in institutions and another brother was dead. He had hypotension but no evidence of adrenal insufficiency.

Case 12 The third is from a lad of 16, under the care of Dr B G Parsons-Smith, who has had choreiform movements since the age of 6 with involvement of speech. At times the movements are of an obsessive-compulsive type and he is subject to violent fits of temper. Although a functional element is not questioned it is nevertheless believed that he has an organic disease of his basal ganglia. The EEG reveals an abnormality over the temporal lobes as is seen in certain biochemical disorders. There is no intellectual backwardness, there is no family history, all investigations for Wilson's disease have proved negative and there is no history of rheumatism.

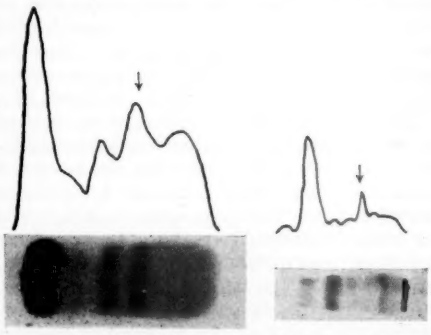

Fig 7

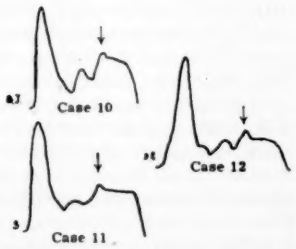

Fig 8

These studies are admittedly incomplete for the lipoproteins were not specifically examined: the resemblance of these profiles to each other may be fortuitous. In 2 cases of 'degenerative chorea' de Rissio *et al.* (1957) have noted, on paper electrophoresis, a conspicuous increase of β-globulin in the C.S.F. but in the serum the changes were notable only for a slight increase in the γ in one of them. It is premature to speculate on the nature of the β-globulin increase in these degenerative diseases of the central nervous system, whether they represent tissue damage or an immunological response, and on how closely they are associated with the lipoproteins.

Brain Proteins in the Cerebrospinal Fluid

An excess of the α fraction, and especially the α_2, we have learned to associate both in serum and C.S.F. with tissue destruction. Are the α-globulins in the C.S.F. which we see in autochthonous patterns, as for instance in multiple sclerosis, derived from cells disrupted during the pathological process or are they actively produced by plasma cells as an immunological response or by other cells as part of the repair process? Kiyota (1959), using free electrophoresis, found an increase of albumin and α-globulin in the white matter in cases of cerebral œdema, and concluded that an excess of the α fractions in the C.S.F. spelt tissue destruction. However, one cannot exclude the possibility that an α-globulin is secreted by plasma cells because it is known sometimes to be associated with a myeloma.

The idea that some of the C.S.F. originates in the brain itself is an old one and was freely envisaged by Weed (1914) and several others since, including Lups & Haan (1954) and Davson (1956). Recent experiments by Bering (1959) on dogs, in which the production of C.S.F. was measured both against oxygen metabolism and in relation to the cerebral circulation, demonstrate that the choroid plexus cannot account for all the fluid.

Brain proteins undoubtedly find their way into the C.S.F. The pre-albumin concentration of ventricular fluid for instance is said to be higher than that of lumbar (Bauer 1953; Steger 1953) and it appears that it does not follow the serum level (Aly 1957). Schaltenbrand (1956) believes that it is added to the ventricular system from the neural parenchyma and this view is supported by Booij (1957, 1958) who finds this fast-moving fraction in homogenates from many, although not all, parts of the brain. In these comparative studies between brain and C.S.F. the τ fraction of Bücher is revealed in all situations as the highest peak, which supports its encephalogenetic origin. There are three sources from which protein could be added to the fluid as it finds its way down to the lumbar theca: (1) The ependyma of the lateral ventricles, (2) the choroid plexus of the third and fourth ventricles and (3) the Virchow-Robin spaces. There seems little doubt that the last contributes most but that is no reason to deny the possibility of a role to the ependymal cells in the exchange of metabolites between the brain and the C.S.F. although it must be admitted that there is little evidence of it. Schalekamp (1961), however, demonstrated the presence of a brain-specific protein in the 50-hour chick embryos whose neural tissue consists almost exclusively of epithelial cells.

Immunity Mechanisms Concerned in Pathogenesis

Since Turnbull & McIntosh (1926) gave the first histological account of postvaccinal encephalitis a wealth of evidence has collected to show that the post-exanthematous encephalopathies are to be regarded, not as extensions of the original infection nor as evidence of activation of a dormant virus, but as due to the presence of a substance which, emerging from the cerebral veins – often in so doing damaging them conspicuously – induces myelinolysis or some other form of tissue destruction. Many workers have shown how extracts of heterologous brain with suitable adjuvants and homologous brain with vaccinia can produce a similar pathology, while Paterson (1960) has demonstrated the immunological character of this allergic encephalomyelitis by successfully transferring it in lymph node extracts from a donor rat, sensitized to spinal cord, into rats rendered tolerant to the donor rat's splenic cells.

In recent years a disease comparable to allergic encephalomyelitis has been seen in man following the administration of therapeutic substances containing nervous tissues (Uchimura *et al.* 1956, Seitelberger & Jellinger 1958, Jones 1958), but few would be willing to equate this condition with multiple sclerosis, a disease which in spite of some overlap with diffuse sclerosis and neuromyelitis optica is distinctive clinically, geographically and pathologically. Moreover in multiple sclerosis there is to our knowledge no local lymph node response to any sensitizing antigen. That the mechanism is similar to that in the allergic disease is beyond cavil so the quest for the responsible antigen, be it of recent or past account, must go on. Pette (1960) reminded us that, in the experimental disease at any rate, the demyelinating agent is not the antigen itself but is something formed as a result of the antigen's impression on the reticuloendothelial system. The peculiarity appears to reside therefore in the host and one imagines that, given sufficient antigenic stimulation the responding clone produces antibody which in some way attacks the cerebral tissue of the host. In multiple sclerosis, if one seeks an analogy, one would need to postulate either an

antibody still in circulation prepared previously against an antigen which had specifically attacked the brain, or an antibody, prepared against some other antigen, which happens to be myelinolytic. In either instance the antigen would need to be rare and geographically peculiar. The alternative view might be that the antigen is common enough but that an indiscretion on the part of the clone, perhaps geographically or even genetically determined, renders an otherwise legitimately formed antibody fortuitously myelinolytic.

An allergic type of pathology is common to several brain diseases amongst which we shall instance two others, Behçet's disease and general paralysis. In spite of a certain resemblance of the skin lesions of Behçet's disease to those of herpes simplex and of claims to have isolated a virus (Alm & Öberg 1945, Sezer 1953, 1956, Evans *et al.* 1957), some of them supported by reproduction of a not dissimilar disease in rabbits and mice, many observers remain sceptical of its infective nature. Histologically it has little in common with multiple sclerosis, the lesions consisting for the most part of small softenings, probably post-thrombotic, scattered throughout the grey and white matter with no primary demyelination and no gliosis. However, in spite of the differences one sees a common immunological pattern of disease often associated with a first zone Lange curve in the C.S.F., the periodic expression in both instances being through those very delicate and thin walled cerebral blood vessels, the antigen when modified by the reticuloendothelial system proving myelinolytic in the one and (probably) thrombogenic in the other.

It is not known why only a minority of syphilitics develop general paralysis but the idea that the rarity of this complication in the tropics is due to the tonic effect on the skin of sunlight dies hard. As in other diseases the rival claims of climate and race in favouring immunity have never been settled. It is, however, generally agreed that inadequate treatment is more likely to be followed by serious tertiary manifestations than is no treatment at all and that tertiary lesions constitute a form of allergy, the spirochætes often being scanty in numbers. The jumbled-up appearance of the nerve cells has been attributed to vascular proliferation and the varied forms of degeneration to ischæmia (Merritt *et al.* 1946). No toxin has been demonstrated and the severity of the cortical disease is not related to the number of spirochætes. However, it appears that the antigen, as modified by the reticuloendothelial system, has succeeded in traversing the capillary walls and in causing neuronolysis.

In the course of evolution the brain has claimed no lymphatic protection from the outside world for teleologically it appears unnecessary. Infective agents reach it through the blood stream and only rarely by contiguity from a focus of infection. A unique feature of the brain is the delicacy of the blood vessels which are peculiarly susceptible to control by corticosteroids. When that viable barrier is penetrated by protein complexes, exogenous or endogenous, lytic mechanisms become possible. Perhaps that is why the brain so often becomes involved when systemic infections are in an allergic phase.

Burnet's hypothesis of clonal selection was conceived to explain certain facts of immunity which were difficult to fit into the earlier theories, such as homograft immunity, tolerance, autosensitivity processes and the immunity which the subjects of agammaglobulinæmia can acquire after viral infections. It includes the basic biological concept that the capacity for antibody production is transferable to descendant cells. Nossal (1958), in his cytological study of animals immunized against two antigens, found that none of the plasma cells he examined produced more than one sort of antibody. The hereditary character of the globulins they produce is indicated by the findings of Dubiski & Kelus (1961) who, when investigating the sera of 1,000 rabbits derived from 11 separate populations, noted considerable differences between them and were able to distinguish in the γ fraction at least 5 iso-antigens. Burnet thought that the production of antibodies is determined by clones of cells which are themselves evolving in response to antigens and, as in all forms of life, mutants are continually appearing, some of them, unless suppressed, giving rise to pathological states.

The presence in Africans of neutralizing antibodies to the virus of St Louis encephalitis and of a partial cross-immunity between it and West Nile fever – and there are other examples – is understandable once we recognize the possibility of mutation taking place in a virus and of adaptation on the part of the antibody-producing clones of the human host. In neurotropic viruses we see so often a high rate of infectivity, as shown by the appearance of antibodies, with a low case incidence suggesting periodic subclinical assaults. There are many antibodies to be found in healthy persons against the commonly occurring viral and bacterial infections and only occasionally against plague, cholera, syphilis and the enteric group (Schultze 1959). Some may be natural antibodies, Jerne's explanation of them being that they just chanced to have configurations complementary to a particular antigen.

Thirty years ago the word immunity had come to mean the response of a living organism to a foreign protein. To-day it has a wider connotation if we accept the idea that during embryonic life

the evolving clones of cells produce globulins with determinants for the host's own proteins, which globulins are, however, suppressed. The implication is that throughout life any unusual protein produced by a mutant cell is a potential antigen. During early postnatal life and in the decline of life when mutants have their greatest opportunity of expression we may expect to find disease due to cell aberration, and various forms of neoplasia, particularly the epithelial group, have been explained on this basis. Within the central nervous system the problem is more difficult because cell turnover appears not normally to occur. The neurosurgeon will wonder in what way the ganglioneuromas could arise postnatally as a result of mutation and a lack of suppression. For the same reason it would be difficult to visualize a degenerative disease of the central nervous system due to mutation of nerve cells. Mutation of genes within a cell which is itself perennial could conceivably take place and so enzymic anomalies and deficiencies within individual cells of the central nervous system, especially the more highly organized of the neurons, might be expected with increasing age. However, when large numbers of cells degenerate, as in Huntington's chorea or in some other form of systemic atrophy (Spatz), a more likely explanation might be the failure of an extraneuronal substance necessary for the metabolism of that particular group of cells: thus what is sometimes explained on the basis of abiotrophy of certain perennial neurons may turn out to be due to the emergence of mutants elsewhere which fail to produce essential metabolites and which may even stimulate the formation of antibodies. A study of immunity mechanisms in such diseases might help to throw light on these problems.

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Section of Proctology

President R W Nevin TD FRCS

Meeting November 23 1960

President's Address

A Review of Granulomata of the Large Intestine

by R W Nevin TD FRCS (*London*)

The first paper of real interest on this subject was read by Mr Berkeley Moynihan – as he then was – before the Medical Society of London in 1906, entitled 'The mimicry of malignant disease of the large intestine' (Moynihan 1907). He described 6 patients on whom he had operated in the belief – both clinically and macroscopically – that he was dealing with cancer of the large bowel. There are careful and vivid descriptions and in the light of our present knowledge it seems probable that 1 of them was a villous papilloma of the rectum and that 2 were diverticulitis of the sigmoid colon. One of the remaining 3 presented with a large mass in the transverse colon, thought to be an inoperable growth, but this disappeared, with narrowing of the distal limb of the ileum, after ileosigmoidostomy. This was almost an exclusion operation and the case was probably one of Crohn's disease. From the descriptions it is not possible to say whether the others were Crohn's disease or localized colitis.

In 1909 Braun gave a description of a series of cases and classified them. In 1917 Telling and Gruner clearly described diverticulitis and extracted it from the group of non-malignant colonic lesions, although diverticulitis could not be proved pre-operatively until barium enema examination became generally available after the 1914–18 war.

In 1925 Frei – by his intradermal test – was able to separate lymphogranuloma inguinale from other granulomata of the rectum. In 1931 Mock drew attention to interference with blood supply of the bowel – especially by trauma – as a cause of non-specific granuloma. In 1932 came Crohn's first description of his disease (Crohn *et al.* 1932) in which he only referred to the small intestine.

I quote from the most recent of his works:

'It is a non-specific inflammatory disease, one of the larger group of intestinal granulomata, a process affecting mainly young adults and characterized by an acute, a subacute and a chronic phase of necrotizing, ulcerating and cicatrizing inflammation. The disease is further marked by its tendency to fistula formation within adjoining loops of the small and large bowel, by external fistulæ to the abdominal wall and by frequent rectal suppurative complications. A disproportionate increase of connective tissue may and frequently does lead to intestinal stenosis and obstruction. Clinically, the disease is featured by fever, diarrhœa, loss of weight, a secondary anæmia, and the formation of an intra-abdominal mass, constituted by approximated loops of inflamed intestine, frequently joined together by internal fistulæ' (Crohn 1958).

In 1939 Hadfield described the histology of Crohn's disease and we still use this to identify the lesion. The appearances, he said, are

the result of hyperplasia of the lympho-reticular tissue leading to obstructive lymphœdema. The lymphadenoid masses vary in size, the largest forming cellular aggregates 3–4 mm in diameter, visible to the naked eye. The smallest are 0·4 mm in diameter and microscopic in size. In three-quarters of the cases these cellular nodes are scattered evenly through the œdematous submucosa, there being 8–18 to the square centimetre. They show considerable cellular activity, a characteristic cellular response in a variable number of germinal centres making up a nodule of lymphadenoid tissue. The affected germinal centre is later replaced by proliferating endothelial cells with weakly staining nuclei.

In the midst of the cells constituting endothelial aggregates it is usually possible to find a Langhans' giant cell which, when mature, resembles the giant-cell system of miliary tuberculosis, but when this system has reached its full development all proliferation apparently ceases.

Never has the slightest evidence of caseation been seen. Some of the cells contain crystalline masses of various shapes and sizes. Probably the most arresting histological feature is the presence in the regional lymph nodes of a clear-cut specific formation of giant-cell systems identical with that of the thickened mucosa. The natural retrogression of this lesion can best be studied in this situation.

When viewed as an isolated and static histological

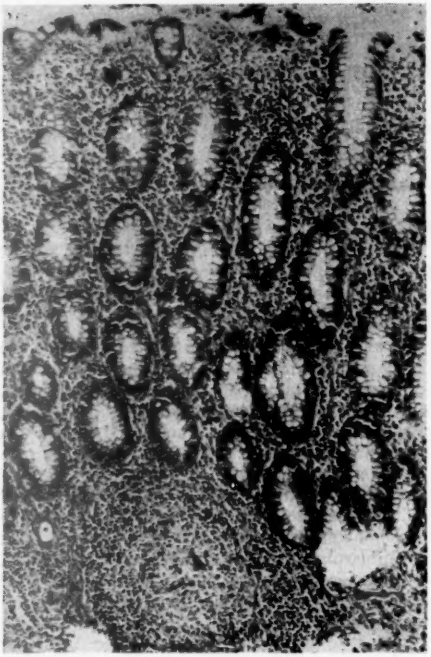

Fig 1 *Rectal mucosa in Crohn's disease. A small follicle composed of endothelioid cells and giant cells, and surrounded by lymphocytes, is situated deep in the mucosa (bottom centre). There is no central necrosis in the follicle. H & E×75*

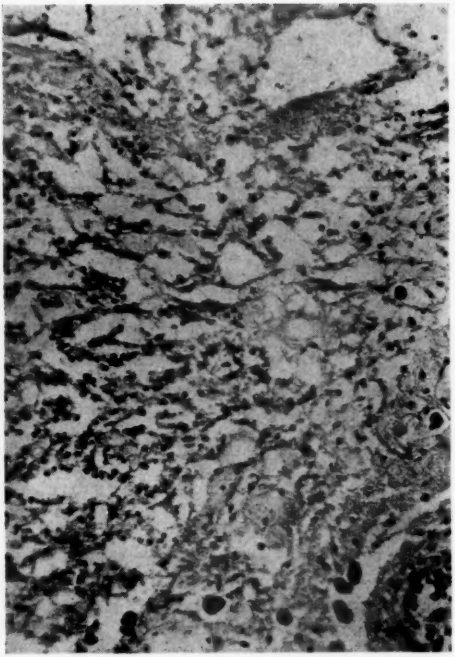

Fig 2 *Amœbic colitis. There is ulceration (top) and complete destruction of glandular tissue. Six amœbæ are seen deep in the mucosa (bottom centre). H & E×180*

picture the giant-cell systems, both in the glands and the bowel, are indistinguishable from those of tuberculosis, but the absence of caseation and of acid-fast bacilli force one to doubt its tubercular origin (Fig 1).

From the purely histological aspect, the appearance, evolution and retrogression, the giant-cell system of Crohn's disease more resembles the tissue reaction of Boeck's sarcoidosis than of tubercle infection (Hadfield 1939).

One may add that there is no record of a case of Crohn's disease going on to a generalized sarcoidosis.

I would like to make a plea that this condition be known as Crohn's disease wherever it may occur.

Fifteen years ago in 1945 Mr Eric Crook gave his Presidential Address before this Section on non-specific intestinal granuloma. He dealt with the small bowel as well as the large and the cases he described were mostly those of Crohn's disease affecting the ileum, but sometimes affecting the large bowel as well. He emphasized the importance of Hadfield's histological description and went on to cite diverticulitis and lymphogranuloma inguinale as examples of lesions to be separated from the mass of conditions of undetermined pathology which constitute the non-specific intestinal granulomata. He concluded by pointing out that we are left with a condition mainly affecting the ileum and less frequently the colon, the problem of whose ætiology has not been completely solved (Crook 1946).

Subsequent papers have consisted largely of case descriptions.

The granulomata of tuberculosis and actinomycosis can be recognized by their characteristic histological appearances and by the demonstration of the causative organism. Actinomycosis tends to produce masses in the colon and to leave the mucosa intact. Syphilis in the bowel is rarely seen, although I have once seen a primary syphilitic lesion of the rectum which was initially thought to be a carcinoma on account of the bulk of the reaction produced. A 'dark ground' examination proved the diagnosis.

The granulomata of amœbiasis and schistosomiasis have no distinctive cellular characteristics and are only recognized histologically if the amœbæ or ova can be demonstrated (Fig 2). It is unnecessary to recite the clinical and other charac-

teristics of these two conditions, although the importance of their diagnosis can never be exaggerated. If the possibility is kept in mind they will not be overlooked. If a strong suspicion of amœbiasis remains although the diagnosis cannot be proved a course of emetine should be given before any exploratory surgery is undertaken. *Schistosomiasis mansoni* produces granulomatous masses in the colon and rectum which can be felt as such but never seem to produce obstructive symptoms (Fig 3). Unlike the similar condition in the urinary bladder, malignant change is virtually never seen. Bleeding and ill-health result. Treatment with tartar emetic produces a dramatic response. Granulomata which are non-specific from the histological point of view have been found in cases of chronic bacillary dysentery in which the positive agglutination titres have been considered diagnostic.

Brooke (1959) sought to distinguish between ulcerative colitis and Crohn's disease. He asked for the retention of these terms and also that of enterocolitis for a condition associated with steatorrhœa, affecting first the small intestine and only extending to the large intestine later, which might account for some of the cases of so-called right-sided colitis. In distinguishing between the two major conditions he emphasized that ulcerative colitis could be eradicated by a total proctocolectomy, whereas Crohn's disease might recur in the ileum after colectomy.

Lockhart-Mummery & Morson (1960) have described 25 cases of Crohn's disease of the large intestine. In 17 of these cases there was no involvement of the small intestine.

These two recent papers seem to offer the first positive declaration of Crohn's disease affecting the large bowel without any involvement of the small bowel, although I am sure that most of us have realized this fact for a number of years.

Lockhart-Mummery & Morson emphasize the importance of rectal biopsy and the demonstration of Hadfield's histological criteria, but are willing to recognize cases which have not these histological characteristics and yet possess the typical macroscopical appearances of great thickening of the submucosal tissues with intramural fissures and granulomatous infiltration of all layers. The mucosa shows more or less localized ulceration and often extensive areas of normal mucosa between the ulcerated areas. They also state that they have never seen Crohn's disease and ulcerative colitis co-existing in the same patient.

A review of recent experimental work includes Mr Geoffrey Slaney's paper at the Meeting of the Association of Surgeons in Birmingham, in April 1960, which showed the importance of an immunological response in the production of granulomata

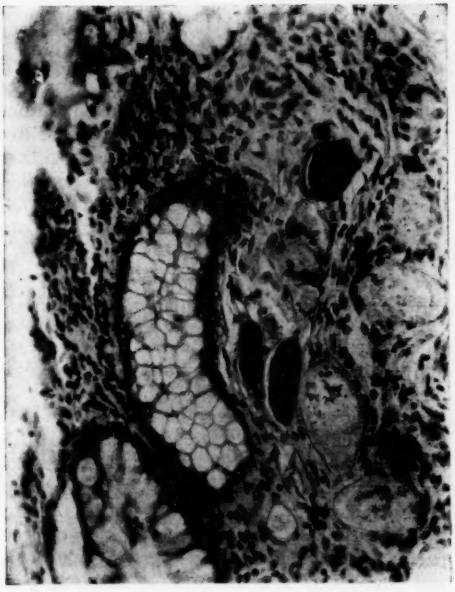

Fig 3 *Schistosomiasis of colon. The mucosa shows superficial ulceration with loss of surface epithelium (left). The mucosa is heavily infiltrated with ova (right half). H & E × 225*

in the intestine. He sensitized rabbits with intravenous injections of horse serum and later performed a laparotomy and injected similar serum beneath the serosa of the small bowel. 93·3% of the rabbits so treated produced granulomatous lesions at the site of injection.

Goldgraber & Kirsner (1958, 1959) in a series of experiments have studied the Arthus and Schwartzman phenomena and have shown that granulomata with or without giant cells are characteristic of the reactions produced in hypersensitive animals and have demonstrated necrosis in the tissues in some cases.

Mills (1957) states that

'after implantation of the virus [of lymphogranuloma venereum] in the rectum an intense proctitis ensues and this stage may last an indefinite time from a few months to several years. This has been aptly called the "prestricture phase" (Spiesman, Levy, and Brotman, 1937). Eventually fibrosis follows the inflammatory infiltration, and stricturing commences. The process of fibrosis is greatly aggravated in the Negro (the so-called "fibroplastic diathesis" postulated by Rosser (1923) and the stricture forms readily.

'The reaction of the bowel to this infection appears to be entirely non-specific and bears many resemblances to that seen in localized ulcerative colitis and in regional ileocolitis. . . .'

It is probable that the actual appearances of the bowel in a number of granulomatous lesions may

themselves be non-specific and may represent phenomena of sensitization.

Some authorities – notably, Goldgraber, Kirsner & Palmer (1960) – feel that it is wiser not to attempt to distinguish between the conditions variously described clinically as regional colitis, enterocolitis, right-sided colitis, segmental colitis, ileocolitis and ulcerative colitis. They find that these conditions tend to merge one into another and suggest that the whole matter be left in confusion.

It is not necessary to understand the ultimate cause of a disease in order to regard it as an entity. Every Member of this Section acknowledges carcinoma of the large bowel as a disease entity, although he knows nothing of its causation.

As a teacher of undergraduates it is one's duty to be explicit and one's critics will say that this must lead to over-simplification at the expense of truth. In spite of this an attempt at precision must be the right policy.

A definition of ulcerative colitis is difficult partly because the term was first introduced in this country to describe patients suffering from chronic diarrhœa who had not been abroad and could not be proved to be suffering from any known dysentery. A number of conditions, which are now well recognized, have been separated off in the course of years and we are now left with this potentially dreadful disease of unknown ætiology which is usually most marked in the left colon and in the rectum.

The early and milder cases are characterized by remissions and relapses but later ulceration which involves the mucosa tends to spread by burrowing abscesses in the submucous layer but rarely involves the muscle layer. A pannus of granulomatous tissue may grow beneath the serosa, but rarely are all the coats of the colon involved as in Crohn's disease.

The colon tends to be thin-walled with vascular granulomatous tissue at the base of the ulcers. Lymphatic involvement is less marked than in Crohn's disease.

There is nothing characteristic or diagnostic in the cellular reaction seen in the histological picture and after removal the disease does not recur.

Watkinson *et al.* (1960) discuss the chronic inflammatory conditions which may affect the right side of the colon.

I think we may agree to separate the cases of Crohn's disease whether the ileum is affected in addition or not.

There seems no histological evidence to suggest that segmental (or right-sided) ulcerative colitis is a different disease entity from diffuse ulcerative colitis which usually affects the left side of the colon particularly. In fact there is some evidence that these segmental or localized cases – if not resected – may become more extensive.

The points of difference between Crohn's disease and ulcerative colitis may be summarized as shown in Table 1.

Table 1

Points of Difference

Crohn's disease	*Ulcerative colitis*
May affect any part of the large intestine	Usually affects the distal part of the large intestine, extending proximally for a varying distance
Commonly affects the ileum	Only affects the distal ileum if the ileocæcal valve becomes incompetent
The submucosa is affected initially. Later there is granulomatous infiltration of all layers, but large areas of normal mucosa survive	The mucosa and submucosa are affected, usually in continuity. The deeper layers are very rarely affected
Histologically giant cell systems present but no caseation	No giant cell systems or endothelial aggregates
No tendency to malignant change	Tendency to malignant change
Does not respond to steroid therapy	Mild cases respond to steroid therapy
Tends to recur after removal	Cured by radical excision

Illustrative Cases

Case 1 Male aged 17

Admitted to St. Thomas's Hospital 9.3.59 as an acute abdominal emergency under Mr R H Boggon. He gave a history of abdominal pain for eight days. At the onset the pain, which was slight, was in the epigastrium and after four days it moved to the right iliac fossa. He vomited on several occasions during this week prior to admission. There was no change in bowel action.

On examination: Temperature 99·6° F. Pulse-rate not raised. Tongue furred and fetor present. A tender mass was felt low down in the right iliac fossa and on rectal examination he was tender on the right side. A diagnosis of an appendix mass was made and he was treated conservatively.

During the next three weeks his condition remained unchanged and his temperature continued to swing, never rising much above 100° F.

He then began to lose weight rapidly and the mass increased in size, felt harder and could be felt on rectal examination.

A barium enema was attempted on 13.5.59 but it was only possible to fill the lower rectum which showed evidence of extrinsic pressure. An intravenous pyelogram on 15.5.59 showed marked hydronephrosis of the right kidney and dilatation of the right ureter above the level of the pelvic brim. The abdomen became slightly distended and he complained of colic.

It was thought unwise to attempt a small bowel barium meal. WBC 20,000 (polys. 88%).

Laparotomy 20.5.59 revealed a large mass occupying the right lower quadrant of the abdomen, which was adherent to the rectus sheath and appeared to include the cæcum. It had a thick fibrous wall and contained necrotic material. It was thought macroscopically to consist of a rapidly growing malignant lesion, but microscopy showed it to consist of granulation tissue containing abscess cavities. There was no evidence of actinomycosis. Initially the lesion appeared to be sterile, but later a sinus appeared from which streptococci were grown. There has never been any fistula formation.

The case was seen by Mr Harold Edwards, on whose advice a prolonged course of penicillin was given. The patient's condition gradually improved and he began to put on weight. Later he was given a course of tetracycline and this was followed by novobiocin. Gradual improvement has been maintained, but his sinus has not finally healed, neither has the mass disappeared completely.

He is now very fit and does a full day's work. A recent assessment included curettage of the sinus and a barium enema which shows that the rectum is slightly displaced to the left and is contracted especially in its upper two-thirds. The rectal wall shows some irregularity.

This throws no further light on the case, which must be regarded as a non-specific granuloma.

Case 2 Woman aged 61
Admitted St. Thomas's Home 5.1.54 with a history of attacks of diarrhœa for six months. Although she was born in Eastern Europe and had lived abroad most of her life she had had no known attacks of dysentery or other bowel trouble.

On examination the cæcum was palpable and the liver was palpable and smooth but no other abnormality was found.

Barium enema showed a filling defect in the ascending colon just above the cæcum.

Laparotomy (9.1.54): The cæcum was distended. A firm constricting lesion of the ascending colon was found just above the distended cæcum. The liver was normal. There was no marked enlargement of lymphatic glands. A right hemicolectomy was performed. *Histological examination* showed fibrosis and some lymphoid hyperplasia in the submucosa of the colon at the site of constriction. The mucous membrane appeared a little atrophic. There was œdema of two regional lymph nodes. No specific cause for the constriction could be demonstrated.

Non-specific granulomatous conditions in the region of the cæcum and ascending colon are well recognized as illustrated by these 2 cases.

Case 3 Married woman aged 70
Admitted to St. Thomas's Hospital on 28.9.60, complaining of diarrhœa which she had had for three months.

On examination she was found to have a posterior fissure in ano with a sentinel pile and small sinus posterior to this. Nodules were present above the fissure. Tubercles and some small ulcers were seen in the rectum with a sigmoidoscope.

Biopsy showed small, rather ill-defined tubercles with caseation in tissue from the anorectal junction which also showed non-specific inflammatory features. Tubercle is the most likely cause although no tubercle bacilli were demonstrated.

Case 4 Man aged 52
Transferred to St. Thomas's Hospital from a country hospital on 8.6.60 complaining of anal pain for two months. This was preceded by two bouts of loose motions. There was no history of injections.

On examination raised firm plaques were present on the anal skin. The lesions were tender and fissures were present.

WR, GCFT, and Frei tests were negative.

Biopsy of perianal lesions showed severe foreign body giant cell granulomata and epithelialized sinus formation.

Proctoscopy and sigmoidoscopy were normal.

It was thought probably to be a case of 'hydradenitis suppurativa', i.e. a chronic non-specific infection of the anal apocrine glands. The condition gradually subsided without any antibiotic treatment.

Case 5 Girl aged 19
Admitted to St. Thomas's Hospital on 19.9.60.

History: Diarrhœa for nine months, with an average of four stools by day and four by night. The stools were dark in colour, there was no obvious blood, they did not froth and were of a 'spongy appearance'. She lost 28 lb in weight during nine months.

On admission she was anæmic and the abdomen was scaphoid. No abdominal masses were palpable. There was an anal fistula with a track extending forwards into the labium majus and much induration of the surrounding tissue.

Sigmoidoscopy showed redness and œdema of the mucosa with some small ulcers.

Barium enema showed that the rectum, sigmoid colon and descending colon were narrowed throughout and the rectum appeared to be rigid. There were multiple filling defects. No ulceration visible.

29.9.60: The fistula was laid open and specimens of the rectal mucosa were taken for biopsy. These showed giant cell systems with epithelioid cells and no caseation.

A diagnosis of Crohn's disease was made.

The patient's condition deteriorated and on 5.10.60 a one-stage total proctocolectomy was performed with an ileostomy. The ileum and jejunum were normal.

There was scattered involvement of the cæcum and ascending colon. The mid-transverse colon, splenic flexure, descending colon, sigmoid colon and rectum were all involved. The lymph nodes of the distal and intermediate groups were markedly enlarged.

Histological examination of the specimen showed focal

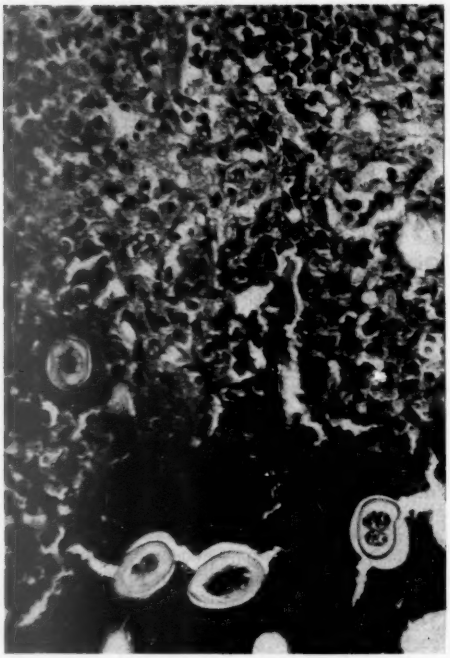

Fig 4 *Granuloma in centre of rectal polyp. At the bottom there are four threadworm ova embedded in darkly-staining necrotic and fibrinous material. This is surrounded (above) by a granulomatous mass of leucocytes, many of which are eosinophil polymorphs. H & E × 360*

mucosal ulceration, extensive submucous inflammation, œdema and fibrosis and scattered giant cell 'tubercles' in all layers. There was no caseation present. The epicolic and ileocolic lymph nodes showed marked œdema of sinuses and occasional 'tubercles' in lymphoid tissue. Sections from the terminal ileum showed some submucosal lymphoid hyperplasia and œdema but no mucosal ulceration. The post-operative course has so far been satisfactory.

If these definitions of Crohn's disease and ulcerative colitis are accepted, there is still a residual group of conditions which are called non-specific granulomata, which perhaps includes those cases which may be called segmental or right-sided colitis.

A list of conditions which produce granulomata is given in Table 2.

Table 2
Classification

Reaction to known physical and chemical stimuli	1. Trauma 2. Foreign bodies 3. Injection of chemical substances 4. Radiation
Structural abnormalities	5. Diverticulitis 6. Congenital malformations
Chronic specific inflammation	7. Tuberculosis 8. Syphilis 9 Actinomycosis 10. Blastomycosis 11. Lymphogranuloma inguinale 12. Chronic bacillary dysentery
Parasitic diseases	13. Amœbiasis 14. Schistosomiasis 15. Worms (Fig 4)
Inflammatory lesions of unknown ætiology	16. Crohn's disease 17*a*. Ulcerative colitis 17*b*. Segmental colitis 18. Non-specific granulomata

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Section of Physical Medicine

President R W Windle MD

Meeting October 12 1960

Discussion on the Treatment of Cerebral Palsy

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Critical Evaluation of Treatment of Cerebral Palsy

The progress of patients having treatment and training may be assessed by writing down details of their motor performance. One can be more stringent than this by recording motor performance on film, at intervals of time, in standard situations, and seeing in a few minutes changes that have come about over many months. But how can one know that the improvement which may (or may not) be seen in records or on films, is because of, independent of, or even in spite of, the treatment that has been given? Because those concerned in treating illness of any kind want their treatment to succeed, they are apt to attribute any improvement to their therapeutic endeavours; and the more personal the relationship between the child and therapist, the more is judgment likely to be warped.

Cerebral palsy symptoms may sometimes be so flagrant in early infancy that a bad prognosis is given – and yet it occasionally happens that the gloomy forecast is confounded. I have made this pleasant mistake often enough to wonder if I have misinterpreted neurological signs in early infancy. I certainly do; but serial cine films bear out the fact that an infant depressingly stigmatized by stiffness and opisthotonus (for example) may yet be toddling quite nimbly at 2 years. In cases of this kind I do not believe treatment has played any important part in recovery. With less dramatic improvement, appearing gradually over the years of sweat, toil and tears, it is uncertain exactly what treatment has achieved.

One Critical Method of Treatment Assessment

In this welter of uncertainty, an objective test of the effect of some treatment procedure is welcome. Such a test has been carried out in the Department of Electrophysiology at Great Ormond Street.

This test is the poly-electromyograph (poly-EMG) (Pampiglione 1959). An eight-channel display can provide a qualitative and quantitative record, on paper, of a motor disability before and after some therapeutic procedure. Figs 1 & 2 are from a patient of mine with torsion spasm and the

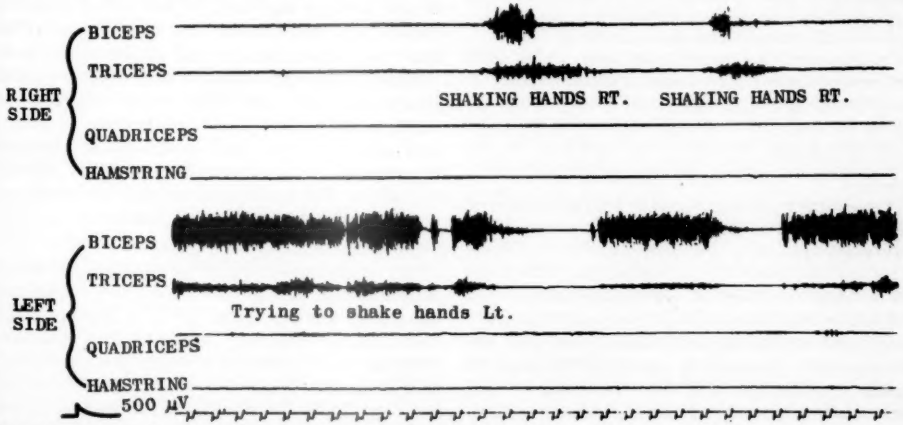

Fig 1 *S T, girl, aged 12½. Pre-operative poly-EMG, 29.4.59*

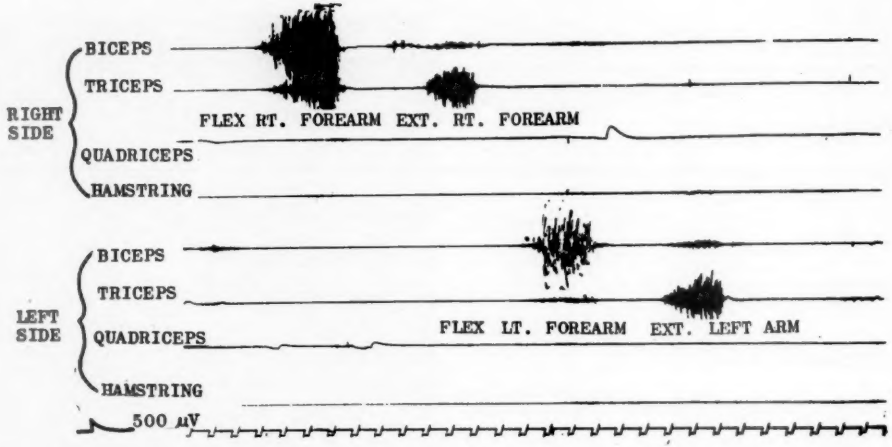

Fig 2 *S T, girl, aged 12½. Poly-EMG 16.10.59. Left chemothalamectomy was carried out on 30.4.59*

poly-EMG records, made by Dr Pampiglione, will appear in a paper of his to be published in the *Cerebral Palsy Bulletin* in 1961.

Case report An adopted girl, born in November 1946. The family history is unknown. When she was aged 3, the left leg became clumsy soon after recovery from measles, but the disability remained fairly static till she had mumps at the age of 8. Thereafter dystonia increased in the left leg and began to spread to other limbs. In 1959 she was investigated in the Neurological Department at Great Ormond Street, and in April 1959 Mr Kenneth Till performed chemopallidectomy with marked reduction in dystonia on the left side as is illustrated by Figs 1 & 2.

Fig 1 is part of the poly-EMG record made before operation. Shaking hands, using the more dystonic left hand, makes little difference to the record which is dominated by spontaneous dystonia activity. But when she uses her right hand, the spontaneous dystonia activity in the left biceps and triceps is inhibited.

Fig 2 is part of a record made six months after chemopallidectomy. Spontaneous dystonia activity in the left biceps and triceps has virtually disappeared. On flexing the right elbow, the extensors (triceps) are abnormally active. On extending the right elbow, the flexors (antagonists) start contracting before the elbow extensors.

[These records are reproduced by kind permission of Dr Pampiglione and the Editor of the *Cerebral Palsy Bulletin*.]

The Service Provided by a Cerebral Palsy Unit

The team concerned with cerebral palsy problems should seek to treat the whole family unit and not just the child. Counselling parents about how to handle and manage and rear the child is one obvious and important service. To the counselling of parents and the provision of opportunities for them to meet other parents with cerebral palsied children, one can add instruction of parents. In this day of 'do it yourself' outfits of all kinds, the policy of teaching the mother to be her own physiotherapist (in the widest sense of that term) pays handsomely, particularly with young children. The parents need to know what to do to combat contractures (when the cerebral palsy is of a kind likely to develop them) and how to provide opportunities for developing motor skills in the child. They also need encouragement.

Disadvantages of a Cerebral Palsy Team

Although treatment of the cerebral palsied child calls for a lot of teamwork, great disadvantages follow if the team is ill-matched. The pædiatrician, orthopædist, physical medicine specialist and neurologist may differ in their views on treatment. If the team is scattered between hospitals and special schools, the opportunities for disagreement are much greater. Thus the orthopædic surgeon may abolish Achilles tendon contractures by manipulation and serial plasters to facilitate walking, only to have his work undone by a team member who takes the child off its feet, because the dogma is held that a child must not be allowed to walk until it has learned to crawl correctly.

Treatment of Associated Defects

There is no doubt about the value of treatment provided for many of the defects commonly associated with cerebral palsy. I have in mind correction of hearing defects by hearing aid, listening training and lip reading, and the correction of ocular defects by surgery and orthoptic training. The work of the educational psychologist undertaking remedial teaching of cerebral palsied children with dyslexia and dysgraphia is

of much the same kind. The speech therapist seeks to do for the speech movements what the physiotherapist seeks to do for movements of manipulation and locomotion.

Treatment of Spasticity

Hypertonus: Spasticity and rigidity can be particularly crippling when they so lock the joints of a limb that voluntary actions of which that limb is capable are prevented. The resistance to active and passive stretch is due to the over-activity of the muscle spindle or gamma loop system. It is gamma rigidity – due to over-activity of the gamma motor neurons which over-sensitize the muscle spindle receptor organs.

(1) *Procaine into motor points:* One kind of treatment of gamma rigidity is to interrupt the gamma loop system. This can be done by repeating what Walshe did in 1924–namely the injection of motor points of muscles with procaine. This is effective because procaine selectively blocks the smaller gamma motor nerve fibres and spares the large and more resistant sensory and motor fibres. It can relieve spasticity and rigidity without lessening voluntary power – but is impracticable as a method of treatment because of its transient effect.

(2) *Drugs:* It would be delightful if we had a drug which was safe, could be swallowed and which had a selective blocking action confined to some part of the gamma loop. Perhaps one day such a drug will be found: but meanwhile a host of drugs have been used for the relief of hypertonus and claims made on their behalf. These include barbiturates, curare, Myanesin, chlorpromazine, zoxazolamine, methylcarbamol, meprobamate, thiocolchicoside and so on.

(*a*) *Trancopal:* Carter (1959) published a glowing account of the value of chlormezanone (Trancopal) in the relief of spasticity. This drug belongs to the methazanone group of compounds. It has been shown to exert an inhibitory or depressant effect, in experimental animals, upon polysynaptic pathways at subcortical and spinal levels, and to have potent relaxant effects on skeletal muscle. At Great Ormond Street, we have made a double blind trial of this drug on 28 cerebral palsied children with pyramidal and extrapyramidal syndromes. Twenty-one of these patients completed the two months' trial. There was no significant difference between the effects of the drug and of dummy tablets.

(*b*) *Tigloidine:* The *Lancet* (1960), in an annotation about the relief of spasticity, commented on O'Rourke's publication on tigloidine (O'Rourke *et al.* 1960). It recommended preliminary trial with this drug before employing procedures involving risks of irreversible damage. Tigloidine is a close homologue of atropine; but in therapeutic doses it has no parasympatholytic side-effects. Of O'Rourke's 21 patients, all of whom had spastic paraplegia with muscle spasms, only one derived no benefit. I have used this drug on a small scale, in the recommended dosage (up to 30 mg/kg body weight) in adults with spastic paraplegia, in children with athetosis, with torsion spasm, and with spastic diplegia. There has been no detectable improvement so far.

In the evaluation of these two drugs, and others with relaxant properties, poly-electromyography would seem to have prospects of offering help. The makers of tigloidine have kindly supplied me with a preparation of this drug suitable for intravenous injection. Dr Pampiglione and I intend to observe any changes in the poly-EMG which may follow the injection of tigloidine.

(3) *Injections into the theca and other structures:* Intrathecal injections of alcohol and of mephenesin have never become popular for relieving spasticity because of undesirable side-effects which include loss of sphincter control. In 1952 Munro claimed that repeated injections of procaine into the sciatic nerve could have long-lasting relaxant effects. In 1955 (and in later publications) Maher described the value of intrathecal injections of phenol in lipid solution, for the relief of intractable pain; and in 1959 Nathan, also Kelly & Gautier-Smith, described the application of this technique for the relief of hypertonus. The result of this procedure is a chemical rhizotomy which may be complete or incomplete. When incomplete, the hypertonus may be reduced or abolished, voluntary power being preserved. It is possible that in the incomplete cases, the gamma fibres, being smaller and more vulnerable to the action of phenol, may be those mainly knocked out, with consequent interruption of the gamma loop system. At first sight it seems that here is the ideal method of abolishing hypertonus in spastic diplegia and hemiplegia. But, although I have used this method of treatment in adults and children, I have not the courage to use it in diplegics or hemiplegics because: (*a*) Too much may cause flaccid paralysis. (*b*) If too little is given the procedure can be repeated; but injection becomes less and less effective – probably because reactionary arachnoiditis acts as a barrier between the nerve roots and the phenol. (*c*) If the injection is too high it may affect just those muscles which should remain unaffected. For example, the quadriceps may relax but the spastic hamstrings, now unopposed, hinder extension of the knee on walking so that weight-bearing is impossible without support. (*d*) If the injection is too low, it may paralyse the bladder.

It may be that with further experience of this and related techniques, hypertonus will be controlled in cerebral palsied children, but there is a long way to go yet.

Treatment of Involuntary Movements

Just as the intrusion of hypertonus can grievously hinder the performance of voluntary actions, so too can the intrusion of involuntary choreo-athetoid movements play havoc with motor performance.

(1) *Stereotactic procedures:* When Irving Cooper showed cine films here, in September 1958, of patients with parkinsonism and torsion spasm treated by chemopallidectomy, it seemed that this might be just the answer to the problem of abolishing the involuntary movements of choreo-athetosis.

About this time the neurosurgical department at Great Ormond Street began performing chemopallidectomy on athetoid children. The operation was carried out by Mr Till who had spent some time with Cooper in New York. In none of the 8 cases selected did chemopallidectomy or chemothalamectomy prove successful. This failure contrasts with the striking success which Mr Till has had with this operation in children with torsion spasm and adults with parkinsonism.

(2) *Topectomy:* Another operation designed for the relief of involuntary movements was carried out fifty years ago by Sir Victor Horsley at The National Hospital, Queen Square. He performed topectomy, ablating the precentral gyrus: but the involuntary movements of athetosis soon returned. Bucy (1951) showed that topectomy could be permanently successful in treating unilateral athetosis provided that both area 4 and area 6 were ablated. This operation has been carried out in the neurosurgical department at Great Ormond Street by Mr Wylie McKissock. The operation certainly has a place in treating unilateral, or mainly unilateral athetosis; but it is not often that one sees patients with athetosis confined to one side and severe enough to warrant major cranial surgery.

(3) *Amputation:* There is another surgical procedure for the cure of choreo-athetoid movements. This is a very unorthodox operation based on the argument that if a patient has a leg severely affected by athetosis, he may be much better off if he parts with it and has an artificial one instead.

Case report A boy had athetosis involving the left leg which greatly limited his walking range and caused much pain because of the extreme varus deformity. I saw him for Mr A T Fripp at the Royal National Orthopædic Hospital and thought him a suitable subject for topectomy; but when cortical stimulation was performed at craniotomy, Mr Wylie McKissock concluded that his 'leg area' was not where it should be, but down in the central sulcus. The way was barred by two cortical veins and, rather than risk harmful effects of dividing them, we thought it wiser to abandon the operation.

Following this Mr Fripp amputated the leg below the knee with excellent results.

This case is interesting for several reasons. Clinically there was difficulty in deciding whether involuntary movements above the knee were due to involuntary contractions of thigh muscles or whether they were passively transmitted to the thigh from the wriggling foot and ankle. Distinction was important because of the need to predict how well he would be able to control the prosthesis. This is just the kind of question that polyelectromyography can answer.

[Two films were shown illustrating the value of topectomy for the relief of athetoid involuntary movements maximal in the right limbs; and of amputation of a severely athetoid leg with subsequent provision of an artificial limb.]

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Mr G Lloyd Roberts (*London*)

Surgery in Cerebral Palsy

The poor regard in which surgical treatment of cerebral palsy is held is due fundamentally to three causes:

(1) Failure to tell the parents that temporary deterioration almost always follows any surgical operation in cerebral palsy: and to impress upon them that an operation is only an incident in the general management of the child the benefits of which may not be apparent for some time after discharge to out-patient care. They must not expect dramatic improvement.

(2) Selection of patients for operation who are unsuitable physically, intellectually or emotionally for any type of surgery. These errors are familiar and need no amplification.

(3) The use of the wrong operation which may be either useless or harmful. Among the useless though theoretically attractive operations is posterior transplantation of the anterior half of gluteus medius to correct an internal rotation gait. This seldom occurs as an isolated disorder of walking and is usually due to the adductors, being associated with a torsional deformity of the femur.

Of the harmful operations one may mention over-enthusiastic adductor tenotomy and neurectomy which may result in a loss of stability or even the ability to walk if this had depended upon contact between adducted and internally rotated thighs.

Nevertheless I believe that surgical treatment has an important place in the management of the brain-injured child, but it must be emphasized that by surgery I mean non-operative methods as much as operative, the choice depending upon a most careful appraisal of the mechanical disability in relation to the child as a whole. Such an assessment in a difficult case can seldom be made in out-patients and few children do not ultimately benefit from admission to hospital before a decision is made in which not only the physiotherapist and ward sisters take part but also on occasion the neurologist, psychiatrist and the parents.

To illustrate some of the principles already outlined I have selected equinus which is the commonest deformity that we meet in cerebral palsy of the spastic type. It is assumed in the discussion that follows that neither athetosis nor any other variety of cerebral palsy exists and that the child is otherwise a suitable candidate for treatment.

Spastic equinus may present before a pattern of walking or even standing is established, succeeding the preliminary period of floppiness which so often characterizes the disease in infancy. At this stage it is fruitless to plan a definitive regime of surgical treatment for it is unwise to begin such treatment until the functional disability is apparent. The walking pattern will be the quotient of the total disability, mental and physical, modified by such treatment as can be given at this age. This cannot be anticipated and sometimes several years must elapse before any decision is made. From time to time children are seen still unable to walk in spite of having undergone multiple operations; this would be avoided if decisions were deferred until walking or at least standing with support was established.

During this preliminary period stretching by the mother under the supervision of the physiotherapy department is usually all that is required for the equinus deformity, if this is coupled with modern methods of physical education. Splints are sometimes necessary but are a mixed blessing, for it is difficult to retain the heel in the position it should occupy and children tend to resent this restriction, especially at night. Furthermore they tend to tear the sheets.

Spastic equinus, however, usually presents as a clinical problem when a walking pattern has become established. Confronted with this we must first decide whether anything needs doing at all. I would suggest that there are four circumstances in which it is better to accept the deformity and simply concentrate on preventing it from worsening: (1) The general physical, intellectual or emotional state discourages any attempt at active treatment. (2) Mild deformity, which is not deteriorating and is compatible with good function may be best treated by a heel raise and a metal toe cap. A toe-raising device with or without 'T' straps and irons is unnecessary and as valueless here as in all other lower limb deformities in cerebral palsy. (3) Equinus associated with diplegia: an anterior centre of gravity and a gait resembling a slow trot is a necessity if the child is to walk at all and should be left alone. (4) Equinus in hemiplegia can also be a vital factor in walking when the heel can be placed on the ground. In these circumstances the tendo achillis through the origin of gastrocnemius hyperextends the knee at each step thus affording stability in walking and so on no account should be interfered with.

The indication for surgical treatment is simple for it arises only when the deformity interferes with function and is no longer under the control of the physiotherapist and the parent. Sometimes there is doubt whether the deformity is due to spasm only and therefore still in theory amenable to further conservative treatment, or structural and not amenable. Examination under anæsthesia will resolve this difficulty and prevent the pathetic spectacle of a dedicated physiotherapist trying to correct a deformity which persists under anæsthesia by attempting to relax spasm in a conscious patient.

If the disability is due to or aggravated by a structural deformity it is clear that action must be taken to correct it, but first it is prudent to try to establish what the main deforming factor is.

Whatever the cause, however, correction by serial plasters under anæsthesia is the first step in almost every case. The plaster which extends above the knee is retained for six weeks and often full correction is attained – its effect being enhanced by the subsequent provision of a night splint to hold the correction obtained at the ankle or a removable splint to hold full extension at the knee on walking. The advantages of preliminary plaster correction are twofold: (1) Correction of fixed deformity in this way may be all that is required if muscle imbalance is thereby overcome, and the correction can be maintained by stretching. (2) Elongation of the tendo achillis in young children often needs to be repeated more than once as the child grows up. This results in progressive weakening of the calf muscle which finally contracts to a small knot lying just below the knee-joint. It is therefore preferable to defer operation as long as possible, being prepared to repeat the plaster correction as often as is necessary until the child is approaching skeletal maturity.

The indications for operation therefore become: (1) Rapid relapse of the deformity after correction in spite of adequate physiotherapy. (2) Failure to obtain correction by plaster.

It is at this point that the type of operation is decided, and in making the choice the primary underlying cause of deformity should be sought – an uncritical approach in which the whole tendo achillis is lengthened by open division will be found to be unsatisfactory in many cases.

For the sake of simplicity the clinical findings after plaster correction may be divided into three syndromes – it being recognized, of course, that there is a measure of association between them, so that the picture may not be as clear cut as this classification indicates: (1) Equinus is uninfluenced by knee flexion. (2) Equinus is reduced by knee flexion. (3) Equinus is produced by knee flexion on walking.

(1) *Equinus uninfluenced by knee flexion* infers that there is a contracture or spasm at both the soleus and gastrocnemius so that open elongation of the tendo achillis is the only course possible. Subcutaneous tenotomy is a dangerous operation in cerebral palsy, for it may result in total rupture of the tendon when the ankle is stretched or as a result of spasm. The result in a growing child is a calcaneous deformity similar to that seen following calf paralysis in poliomyelitis. If spasm predominates it is tempting to perform a selective soleus neurectomy but I have found this to be unrewarding as relapse is rapid. I had hoped that the temporary improvement might allow the physiotherapist an opportunity to teach, in this interval, an improved pattern of walking which might become established but this was not to be. If contracture predominates over spasm it must not be forgotten that weakness of the dorsiflexors rather than spasm of the calf may be the determining factor. (There is a tendency to forget that cerebral palsy is characterized as much by weakness in antagonists as by spasm in deforming muscles.) In these cases gravity, the bed-clothes and weakness of dorsiflexors combine to produce deformity, but frequently the correction of the fixed equinus allows the weak dorsiflexors to function again and prevent relapse. If, however, they remain too weak one of the very few indications for tendon transplantation in cerebral palsy arises, for the tibialis posterior may with advantage be re-routed through the interosseus membrane to reinforce dorsiflexion as in part a dynamic transplant and in part a tenodesis.

(2) *Equinus improved by knee flexion:* In these circumstances spasm and contracture are largely in the gastrocnemius, by virtue of its influence on two joints, the knee and ankle. Again neurectomy is appealing but in practice unrewarding. However, selective division of gastrocnemius high in the calf without interfering with the tendo achillis or the soleus is a simple and successful operation, for it both lengthens the contracted element and reduces the reflex spasm of the gastrocnemius (causing both equinus and knee flexion) produced when this irritable muscle is stretched in walking. This is accomplished without weakening the calf by lengthening the relatively normal soleus. A variation of this operation divides the origin of gastrocnemius from the femoral condyles but the total loss of support to the back of the knee-joint so produced may cause genu recurvatum if the gait depends on extension of the knee for stability. It is curious that this deformity rarely occurs in cerebral palsy in any other circumstances.

(3) *Equinus secondary to knee flexion on walking:* There are three possible causes: (*a*) Involvement of gastrocnemius as discussed already and treated similarly. (*b*) Spasm of hamstrings. Eggers' transplantation of the hamstrings from the tibia to the femoral condyles is an operation of great value. It must usually be combined with a retinacular release of the patella which is frequently tethered distally because of long-standing knee flexion deformity. Failure to overcome this prevents the greatest use being made of the weakened quadriceps after the deforming force of the hamstrings has been removed. Supracondylar osteotomy is but rarely indicated. (*c*) Flexion of the hip resulting in a flexed knee and equinus foot can usually be corrected by traction and maintained in the corrected position by Eggers' hamstring transplant. The reason for this is that the hamstrings no longer expend their force in flexing the knee but become extensors of the hip by virtue of their new attachment to the femur. Subtrochanteric osteotomy is again rarely indicated.

I have tried in considering the common equinus deformity in cerebral palsy to indicate the place of surgical treatment in this disease as a whole, and to show that assessment of the patient and his deformity lies no less in the province of the surgeon than the physician. Even so superficially simple a problem as equinus deformity is one of considerable complexity when cerebral palsy is the underlying cause.

Dr K W Nicholls Palmer (*Colchester*)

Treatment of Cerebral Palsy in Adults

Dr Palmer described the management of handicapped adults in the residential centre at Prested Hall, Kelvedon, Essex, with the aid of a short film and coloured slides (*see Lancet* 1958 i, 842).

Section of Otology

President J P Monkhouse FRCS

Meeting November 4 1960

President's Address

Some Triumphs and Some Problems of Middle Ear Surgery

by J P Monkhouse FRCS (*London*)

The title of this Address, Triumphs and Problems, is chosen to enable me to say something about four conditions. The triumphs are: the treatment of chronic infection of the middle ear and mastoid and the treatment of otosclerosis by means of the operation of fenestration, in both of which we have achieved very great success. The problems are the treatment of secretory otitis media and the treatment of otosclerosis by mobilization of the stapes where, to put it conservatively, our efforts still leave very much to be desired.

Chronic Infection of the Ear

I will start with chronic infection of the ear, but before doing so we should acknowledge the debt that we owe to chemo- and antibiotic therapy. These drugs are a windfall for which we can take no credit, but although much of what we can do to-day would be impossible without their aid we tend to take them for granted. Before the advent of the first sulphonamide streptococcal meningitis secondary to a chronic mastoid infection was not uncommon. To all intents and purposes it was always fatal. I shall never forget a girl of 15 who had a severe meningitis – 5,000 cells in the C.S.F. After clearing out her ear we tried her on the new red Prontosil. In four or five days she was well and that was certainly a milestone.

I inherited from my late chief, F. J. Cleminson, a copy of 'Diseases of the Ear' by Milligan & Wingrave, published in 1911. Reading this book one is surprised by the desire of the surgeons of those days to avoid doing a radical mastoid. There are long sections about cholesteatoma, aural polypi and ears full of granulations, with precise details of the conservative treatment to be applied to each. There is a lot about limited attic surgery – the removal of the outer attic wall, with or without ossiculectomy and usually performed via the meatus. It is admitted that this might sometimes be difficult, but beyond a warning that it was possible to damage the facial nerve there is no suggestion that the operation was considered particularly hazardous. If accidents were indeed uncommon we can only admire the dexterity of those surgeons working as they did with illumination that was probably indifferent and without the help of the wonderful magnification that is available to-day. One would have thought that an open operation would have been much easier and safer but in fact it was generally withheld until the onset of complications by which time it must often have been too late. I can best illustrate the opinion of those times by a quotation. Milligan says:

'While certain surgeons advise operative interference in all cases of chronic septic otitis media of more than one year's duration, others hold strongly that unless evidence of bone disease or of some other complication is present, local treatment with permeatal removal of polypi, granulation tissue, &c., should be persevered with indefinitely. Provided that in chronic cases the mastoid operation could be performed without risk, and with a definite certainty that it would arrest discharge, the arguments in favour of its immediate performance in all intractable cases would be very great. As, however, the operation cannot be performed without an element of risk . . . great care should be taken in the selection of cases for operation. The main objective symptoms indicating operation are the presence of constant fœtid discharge, continuous or constantly recurring pain . . . evidences of cerebral irritation, such as vomiting, vertigo, "chocked" disc or optic neuritis, and impaired movements of the head.

'Attacks of vertigo, transient or continuous . . . Symptoms of cerebral irritation, such as paresis or paralysis of various muscles or groups of muscles, convulsions, mental hebetude, unconsciousness, immobility of the pupil, nystagmus, &c., are indications for the immediate opening up of the accessory cavities of the middle ear, and for a careful search for any fistulous tract leading into the interior of the cranium or labyrinth.' (Milligan & Wingrave 1911, p. 321.)

A rather confused list of signs and symptoms,

but a quite horrifying one. Some of these patients would have had no more than an irritative labyrinthitis and could have recovered, but the majority must already have had either meningitis or a brain abscess.

Opinion changed and by the time of my first recollection there was no fear of the radical operation, though it must be admitted that facial nerves were at some risk and that the after-treatment was long and painful. With a more thorough clearance of disease than we used to attempt coupled with split skin grafting and the aid given by the antibiotics we can now hope to have a dry and healed ear in something under two months. I know that split skin can give trouble but on the whole its use is well worth while. The large cellular mastoid is the one to be feared. However, of late we have heard much about the production of smaller cavities lined by pedicle grafts of full thickness skin, and I have no doubt but that results will continue to improve. But there is now the possibility of improving the hearing by a reconstruction of the middle ear. We owe this to the brilliant work of Wulstein and of Zollner, and it might be argued that the attempt should be made in every case, since success would be a great achievement and failure would leave the patient no worse off than he would have been if we had not tried.

My experience of tympanoplasty is limited, but I am beginning to wonder if this argument is sound. These cases can start off well and then some months later things may begin to go wrong. Grafts break down and perforations appear. This is sufficiently disappointing but it is even worse when the graft begins to bulge, and it is obvious that something, we do not know what, is happening underneath. We can accept these difficulties if it is imperative to try to improve the hearing but if it is not we may find we have merely built in trouble that might never have occurred had the middle ear been left uncovered. The assessment of the condition of the lining of the middle ear is the most difficult part of tympanoplasty. How much must we leave in order to achieve success, and how much must we remove in order to avoid failure? Tympanoplasty is the subject of one of our meetings this year and I shall try to get the speakers to concentrate particularly on this point.

Secretory Otitis Media

This is still a problem. I do not think we know the cause and I doubt if we know the treatment. In spite of many very good accounts I do not think that the prevalence of secretory otitis media, particularly in children, is fully realized. It has been said to be on the increase. This may or may not be so, but of one thing I am sure, the more one looks for it the more one will find. It is not new. Bateman (1957), in an excellent paper given before this Section, mentions that it was described by James Hilton in 1874. As a student I was taught about the hair line indicating a fluid level, but we did not recognize the ear in which the tympanum was completely filled. I can remember wondering why an ear with the drum plastered on to the tympanic wall was only moderately deaf while one with a comparatively normal drum was much worse. They were both called chronic catarrhal otitis media, but the first was obviously a secretory otitis media with a very thin drum and the other otosclerosis. The paper read to this Section by Hoople & Blaisdell (1944) first aroused my interest. The diagnostic features they described were added to by Bateman who was the first to put into words what is a very characteristic sign, the difficulty of illuminating the drum. It is as though one were using an electric auroscope with a poor battery. I would, however, emphasize the diagnostic value of auscultation during eustachian catheterization. There is what might be called the 'blow back'. As one squeezes the bag air goes in, usually rather suddenly and with a rough sound, and then there is a shorter but similar sound just as one has stopped squeezing. It is as though air went in and just a little of it returned, and this sound is pathognomonic of fluid. There is a much more difficult sound described by Hoople & Blaisdell. They say 'It is like the chug of fluid heard in an incompletely filled airtight barrel but even this description is inadequate. It is the most difficult sound in auscultation to recognize and interpret. It is more clearly heard when very gentle inflation is practised. It can easily be missed by a loud blow.' I should like to substitute the word plop for chug and certainly it is only to be heard with a short and very gentle blow, but its recognition can be very useful.

There is also the ear in which the tube sounds clear or, as Bateman puts it, too good to be true. If on other grounds one thinks that there is a secretory otitis media there is no need to abandon the diagnosis because of this finding. It occurs when the fluid in the middle ear is very thick and the air blows around what is almost a dry mass.

It is difficult to speak of secretory otitis media without mentioning blue ears but I am not going to try to consider them in detail to-day. I will only say that I have never believed that blue ears are due to hæmorrhage. All investigations have started off with a bias, being coloured by the colour. The aim has been to explain the occurrence of bleeding and to find a source. These ears are filled with a fluid which amongst other things contains hæmosiderin and cholesterol. I agree that hæmosiderin can only come from blood but there are alternative sources of cholesterol and I am in-

formed on good authority that it would need a great deal of blood to provide the amount of cholesterol that is present, and yet one never finds fresh blood in such an ear, and at operation there is never anything that looks like the source of a hæmorrhage. Birrell (1958) in a fine paper on blue ears, but in which he also refers to secretory otitis media, says 'The two conditions of hæmotympanum and secretory otitis media are different. I am persuaded, however, that the ætiology of the two conditions must be closely allied because the only difference is the presence of blood in one and not in the other'. Surely it would be more rational to say that they are the same condition with some small additional factor that puts colour into the one.

Treatment: In many cases it is sufficient to deal with any infection of the nose or throat, inflate the eustachian tube two or three times and the patient is well. In others we have to add to this puncture of the drum, one, two or three times and again all is well. Then there is the case where all these measures are employed, together with repeated myringotomy with thorough evacuation of the contents of the middle ear, over a period of weeks and months, and still that ear fills up again every time. It makes one wonder if the ear that gets well does so in spite of rather than because of our efforts. It certainly adds force to what seems to be the general, if rather reluctantly accepted, view that it is not all due to eustachian obstruction. From here we must either abandon the case or embark on some sort of mastoid surgery. Birrell, speaking of early attempts of this nature, refers to a report made by Ranger in 1949 on two cases of blue ear, and says that they were cured by a cortical mastoidectomy. There he is mistaken. I did those operations and, as I felt it was essential to provide permanent drainage of both mastoid and middle ear, I used the Heath's operation. I still feel that in either condition this operation is the only one that will guarantee success though I believe now that the essential requirement is a permanent supply of air to the middle ear rather than drainage. I may have been unlucky with the cortical operation but in only one, and that in a boy who can auto-inflate, has it been satisfactory. The others all filled up again within a few weeks.

Stirk Adams (1954), in a paper entitled 'The case for a nitrogen gas secretory function of the epithelial lining of the middle-ear cleft in the production of the "air" in the cleft', postulates that the gas in the middle ear is secreted by the epithelium of the mastoid cells and middle ear and that it does not come up the eustachian tube, the function of which is merely to allow for rapid and gross changes in external pressure. He goes into the theoretical possibilities, cites work of others of an allied nature and can offer as a fact the proved secretion of oxygen into the swim bladder of certain fish, all of which supports his contention. He then devised a method of collecting gas from the middle ear. Gas was found and collected and analysis showed that it certainly was not room air. He was careful to think of and to eliminate possible artifacts, and I feel that he has made out a strong case. I can offer one small observation in support of this idea. When doing a fenestration we leave behind half cells and cover them over with the flap or with skin grafts. A cell in the tip of the mastoid might conceivably retain a communication with the middle ear via some deep chain, but a fairly superficial cell on the posterior wall of the mastoid cavity is most unlikely to do so. In reopening such an ear one uncovers these cells and they look empty. If there was a vacuum they would fill up with fluid, but there is no fluid and therefore they must contain gas and this gas can only have come from the epithelial lining. This concept, though offering no real clue to the primary cause of secretory otitis media, does provide a credible explanation of the disease and explains why treatment via the eustachian tube or by cortical mastoidectomy may fail. What we should do is to persuade the epithelium of the mastoid and middle ear to resume its secretory function but if we cannot do that what is to be gained by a cortical mastoidectomy which merely removes part of the mechanism? There must be gas in the middle ear and we have to get it there even though it be by the abnormal route of a Heath's operation. I expect I am stirring up a hornet's nest, but it will do no harm if it provokes one of you to prove that I am right or alternatively to find the true explanation.

Fenestration of the Labyrinth for Otosclerosis

Here we have a real triumph – probably the greatest that has ever come the way of our specialty – for the first time a worth-while treatment for a commonly occurring and previously intractable form of progressive deafness, a treatment that in favourable and reasonably favourable cases will almost always restore adequate and lasting hearing and one that has completely altered the lives of thousands of patients in this country alone. This operation resulted from the work of many great surgeons over a long period but I should like to salute once again Dr Julius Lempert who gave us the technique that made it a practical possibility. To-day this excellent operation is positively under a cloud. This is partly our own fault, but much more it is the result of misinformed articles in the lay press. Some two or three years ago there were two, one in a daily newspaper and another in similar terms on the follow-

ing Sunday. I only saw the former but reading that article one could only conclude that a fenestration inevitably condemned the patient to a lifetime of misery. We know that this is a quite scandalous misrepresentation of the truth but of late years the attitude of patients towards this operation has certainly changed and I think that these articles must have been widely read and disseminated. There are penalties, and the operation should not be undertaken unless there is a reasonable chance that it will be worth while, but with the exception of a discharging ear which does not occur all that frequently, the penalties are comparatively minor ones and they are readily accepted by the patient in return for hearing. The one real limitation lies in the fact that at times we shall fail, and fail to the extent of making the ear worse. This does not happen very often, perhaps in 5%, but for all that it has a most vital implication: it means that we are never justified in employing this operation on the better ear, and in consequence we can offer no help to the patient whose worse ear is already beyond hope.

Mobilization of the Stapes

It is over nine years since Dr Samuel Rosen revived this idea and presented us with an acceptable technique. Mobilization is a most intriguing operation and we all started off with great hopes. We broke a number of crura, but we had been told that this was inevitable and we had enough successes to make us feel that with more experience we should really get somewhere. Before we had had time to evaluate results we were told to abandon indirect mobilization and to go straight to the footplate. This at once produced much better immediate results in that we were able to mobilize a much larger percentage of bones. However, after some two years of this it became evident that all was not well. There are the unexpected failures. Some, though I do not think all, may have been explained by Venters (1958). He pointed out – and I very much agree with him – that it is not always easy to know what one has done and that intact and mobile crura do not necessarily mean a mobile footplate. But it is very disappointing when one obtains a really beautiful round window reflex with little or no benefit and I do not know how this is to be explained. Then there is the amount of improvement which so often is disappointing. Although on theoretical grounds a successful mobilization should outdo any fenestration only too often we feel that we should have been unlucky if a fenestration had not done better. I would like to illustrate this point with an account of three patients.

Case 1 Mrs A G Fig 1: This patient is not very deaf, and the hearing for high notes is still good. The bone conduction could hardly be better, and if asked to assess the possible result of a fenestration, one would say that she could do really well. At operation the stapes was found to be firmly fixed and was only freed after a prolonged attack on the footplate. Eventually mobilization appeared to be satisfactory, and this was confirmed by the presence of a definite round window reflex. The improvement, shown by the dotted line, is minimal; most disappointing, and even this soon regressed. Fig 2 shows the result of a fenestration, not quite as good as one might have hoped for, but giving her really serviceable hearing.

Case 2 Miss J O Fig 3: This patient is rather more deaf and the high notes are not good. Bone conduction though not perfect is high enough to warrant the expectation that fenestration might give an adequate result. Again the stapes was firmly fixed and required direct mobilization, after which it seemed to be well freed. The round window reflex was not examined.

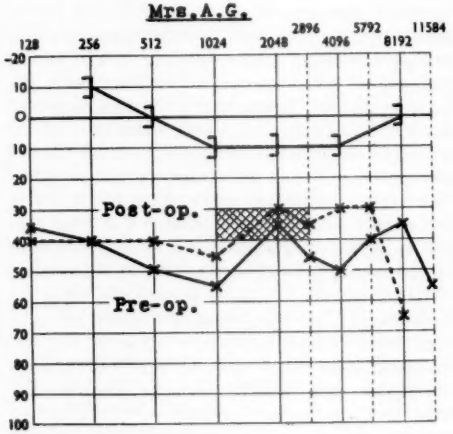

Fig 1 *Case 1*

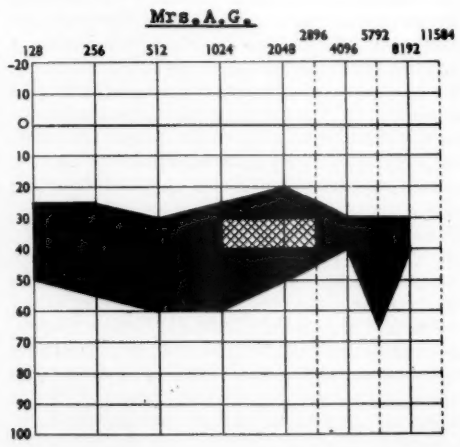

Fig 2 *Case 1*

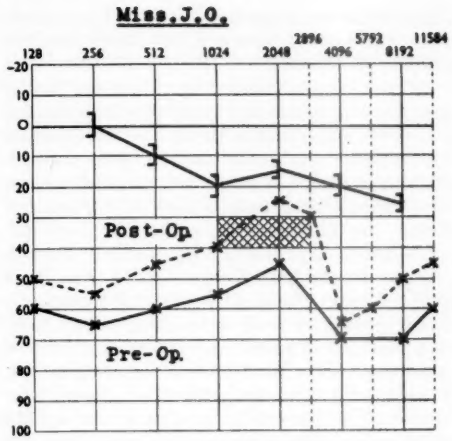

Fig 3 *Case 2*

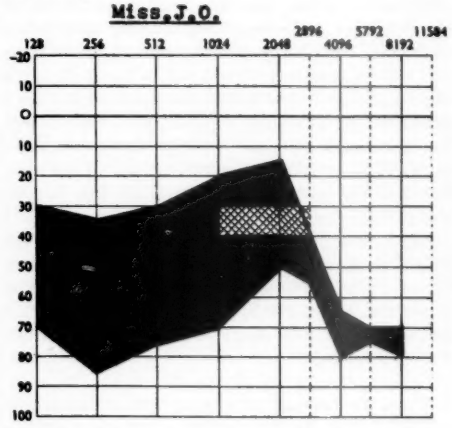

Fig 4 *Case 2*

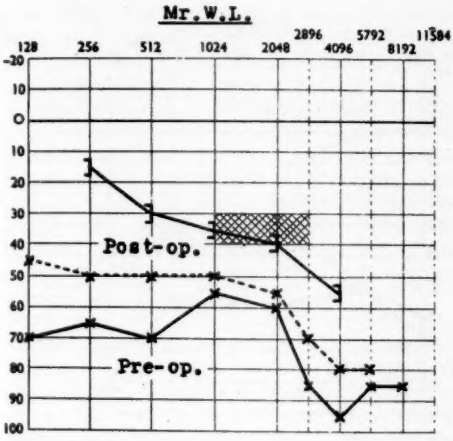

Fig 5 *Case 3*

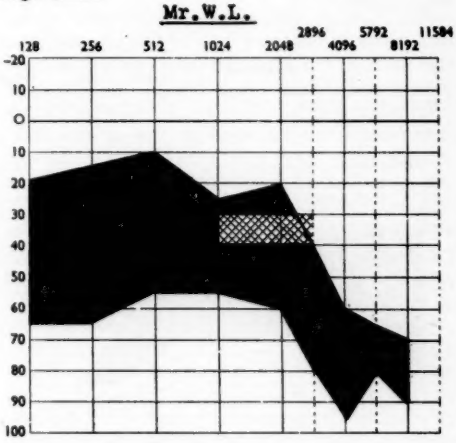

Fig 6 *Case 3*

The dotted line shows the result. There is improvement but it is disappointing, particularly in the low notes. This improvement was soon lost and in eight months, at the time of remobilization, her hearing was worse than before. On this occasion the stapes was very little fixed and moved easily and a definite round window reflex was noted. This mobilization must have been at least as successful as the first one but the hearing remained completely unchanged. Fig 4 shows the result of fenestration which comes up to expectation.

Case 3 Mr W L Fig 5: This patient is in a different category. He has a more advanced deafness, with a marked loss of high notes. Bone conduction is depressed with a steady fall towards the high frequencies. Though he might improve with a fenestration, it is likely that the hearing would come up parallel with the bone conduction and that his hearing for high notes would remain inadequate. At mobilization his stapes was firmly fixed and was only freed by the use of Heerman's gouges. He improved to approximately 50 dB but this was not enough to be of any use, and he asked for a fenestration. I gave him a very guarded prognosis but he insisted. Fig 6 shows the result, which is much better than could have been expected.

One cannot generalize on the strength of 3 patients but I have seen so many similar cases and you, I am sure, will all have had the same experience. However, even when we do succeed the improvement often does not last. It may be going and even gone within a month. Refixation occurs, and if much prodding and hammering has been needed to free the stapes this becomes almost a certainty so that the gain that we expected as a result of direct mobilization has proved to be an illusion. We can remobilize, but I have not found any that lasted better than did the first mobilization. I think that it is generally accepted that feneS-

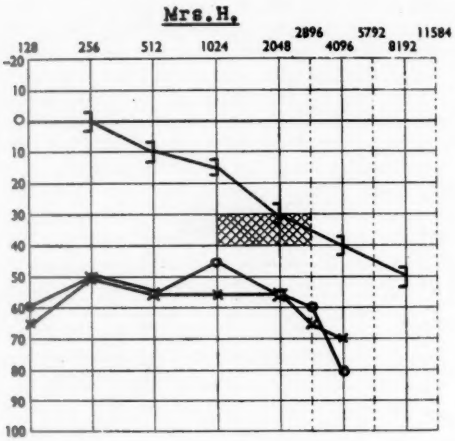

Fig 7 *Case 4*

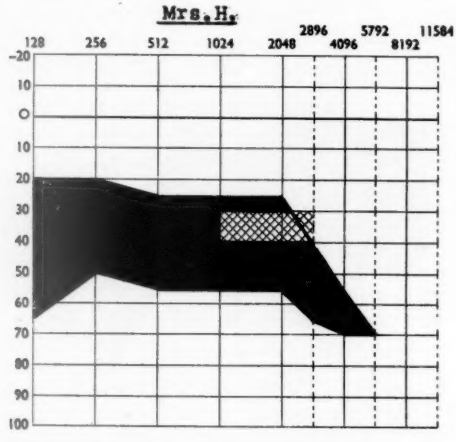

Fig 8 *Case 4*

tration of the footplate is of no value. I have just one patient who has maintained an improvement though it was never enough to be of any use. On one occasion, however, I got help from a fenestration of the footplate though in a different way.

Case 4 Mrs H Fig 7: She has a fairly marked deafness with very poor high notes. Bone conduction shows a severe falling off towards the high frequencies. Not a promising case for fenestration. I tried to mobilize under a local anæsthetic, broke the crura and fenestrated the footplate. The immediate result was dramatic and she could hear really well. It was all gone by next day but I took it to mean that her cochlear reserve was better than I had thought and that if she could hear with a fenestration of the footplate she might hear equally well with a fenestration of the canal. So when it came to the question of fenestration I gave a better prognosis than I should otherwise have done. Fig 8 shows the result. The high tones have improved more than one would have expected.

Of late I have been trying to use the Fowler operation, anterior crurotomy with mobilization of the normal posterior portion of the footplate on the posterior crus. This seems a rational procedure which should avoid the risk of refixation. Unfortunately suitable cases are few and far between. Either the bone is not sufficiently fixed and mobilizes as soon as one tries to cut the anterior crus, or else the posterior part of the plate is not entirely free of disease. It is not an easy operation and I should like to describe one that started off as a Fowler, but ended very differently. The posterior part of the footplate would spring a little, so having cut the stapedius tendon I cut the plate at about the junction of the anterior and middle third and then set to to cut the anterior crus, but in doing this broke both crura. The breaks were close to the plate, and the fractured surfaces of the posterior crus were lying in close apposition and would probably have joined up, but there was not an adequate separation of the ends of the anterior crus, and with completely mobile crura I could not do anything about it. So I tried swinging the crura forward on the incudostapedial joint. This took the anterior crus out of the way, but the posterior crus, though of full length, would not reach the footplate. In desperation I pushed a piece of gel foam between the end of the crus and the plate and this held it there. I remember saying at the time that if it worked it would be a miracle. It did work, remarkably well, and the hearing went up to 20 dB, where it has remained for six months.

There has been a good deal written about immediate results and the improvement that has followed different methods of mobilization, but I have seen little about long-term results and I think that it is time to face up to the situation. My own results may not represent the best that can be obtained by these methods, but I venture to suggest that they are probably not much worse than the average.

There are 129 cases – not a large series, but enough to give a true picture. In 29 the crura were fractured, the majority as a result of indirect mobilization. In 28 mobilization seemed satisfactory but there was no improvement. One can answer this quite easily by saying that in fact mobilization had not been achieved. This might be true in a few cases but I am not prepared to accept it for the majority for the following reasons: (1) The operation notes were considered very carefully and if there was any ambiguity the case was regarded as a fracture. (2) In several

there was a really good round window reflex. (3) I do not think that I should have so completely deceived myself quite so often. I am therefore, going to maintain that these failures are due to inherent defects of the operation rather than to deficiencies of the operative technique. In 72 cases, a little over half of the total, there was improvement. These improvements vary from something that was worth while to, in a few cases, something that was very good indeed.

Of these 72 patients, 38 have lost all improvement and are now back to the pre-operative level. This leaves 34 of whom 12, who all had worthwhile results when last seen, have been lost sight of, and were only followed up for a comparatively short while. Seven have only been operated upon during the last three to eight months. They are included because during the same period others have already regressed and are included in the 38. Fifteen cases still have a worth-while improvement which has been maintained for over one year, and in some up to three years.

There are 19 patients in whom the final result is not known. Perhaps 5 of them, though this may well be too optimistic, either have retained or will retain a worth-while result, and can be added to the 15 making 20 real successes out of a total of 129.

I need hardly tell you that I do not think this operation has justified itself, it certainly has not done so in my hands. What can we do? We could revert to the operation of fenestration of the labyrinth and I am sure that to do so would be much to the benefit of our patients. It would not be easy because fenestration has been so much decried and mobilization so well advertised. Perhaps at the moment we should offer one mobilization as an uncertain but reasonable preliminary step but emphasize to the patient that fenestration may well prove necessary. I am sure that repeated mobilization is quite unjustified. The alternative is stapedectomy. It may be that this is the answer and quite certainly the possibilities of all varieties of this operation must be explored to the full. This, however, does not mean that we should all turn over at once to stapedectomy, to do so would, I think, result in many ruined ears. Stapedectomy differs from mobilization in that it carries a risk. I understand that American short-term figures admit to 8% of damaged ears, and it will be three, five or even more years before we shall know for certain that an ear will tolerate indefinitely the inclusion of pieces of polythene tubing or lengths of wire. We used to put forward a list of the advantages of mobilization over fenestration: (1) Simplicity and comfort and lack of penalties from the point of view of the patient and arising from this the justification for trying this operation on an ear so bad that we would not like to recommend a fenestration. (2) The theoretical possibility of greater gain than can be achieved by fenestration. (3) The safety of the operation. Even if we do no good we can do no harm and because of this safety we can try the ear that is very little deaf and, what was the most valuable asset of all, we can try the better of the two ears, when the other is quite hopeless.

These advantages sounded well, but lose their value if the operation to which they are attached does not achieve its aim. Now suppose we substitute stapedectomy for mobilization not forgetting that we must now accept a risk: (1) The simplicity and comfort, &c., remain. Patients can be a little giddy after stapedectomy but it is not very troublesome and we still have an operation that we can employ on the very bad ear because here the risk does not really matter. (2) The greater gain of hearing. The immediate result of stapedectomy can be very striking and it is possible that this operation will result in greater gains than can be obtained by fenestration. (3) The safety. Now the situation is altogether different. Stapedectomy is not without risk, in fact the risk may be greater than with a fenestration and we are now back to where we started, with no operation that we can justly employ in a case where not even a small risk can be accepted.

I am not going to speak of the various methods of stapedectomy partly because I have not the necessary experience but particularly because Dr Howard House of Los Angeles is to talk to us on this subject in May, when we shall also hear from Mr Simson Hall and Mr Terence Cawthorne. I have delayed this meeting until the end of the Session in order to allow the maximum time for the evaluation of results, and we may then expect to hear an up-to-date and balanced assessment of the position of stapes surgery. In the meanwhile I would suggest that we go cautiously and perhaps remind ourselves that we still have at our disposal that well tried and very excellent operation, fenestration of the labyrinth.

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Section of Surgery

President
Professor Lambert C Rogers CBE VRD FRCS

Meeting November 2 1960

Clinicopathological Meeting

Polycythæmia Due to Hydronephrosis

Harold Ellis MCh FRCS

A fitter, aged 53, was found to have Hb 145% at a routine blood examination. Apart from noting that his abdomen had been getting larger for some years, which he had put down to 'middle aged spread', he was symptomless. He was referred to Dr P C Mallam at the Radcliffe Infirmary, Oxford, who noted him to be plethoric, with blood pressure 170/110, and to have an enormous mass occupying the left side of the abdomen. The spleen could not be felt.

Investigations: I.V.P.: no function left kidney, right kidney normal; calcified shadow left side of pelvis. Urine normal. Cystoscopy: normal bladder, ureteric catheter jammed at 2 cm on the left side. Hæmatological investigations were normal apart from the raised Hb% and red cell count.

Operation (H. E.): Left ureteronephrectomy by the abdominal route, removing an enormous hydronephrotic kidney and dilated ureter, at the lower end of which was impacted a calculus (Fig 1). The right kidney and the spleen were normal. Uneventful recovery. Hb% after two weeks 113%; after three months 77%.

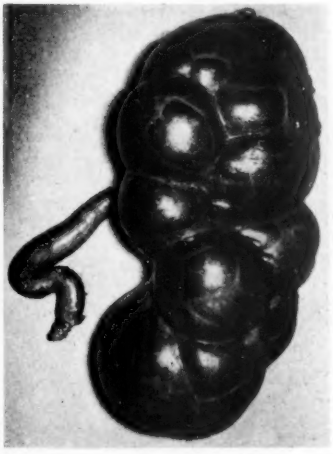

Fig 1 *Gross hydronephrosis and hydro-ureter producing polycythæmia*

Discussion: To date, 52 examples have been recorded of polycythæmia in association with gross renal disease; 42 of these were in patients with hypernephroma (Drivsholm 1960), 6 with polycystic kidneys and 4 with hydronephrosis (Jones *et al.* 1960). Polycythæmia has also been noted in cases of uterine fibroma, secondary deposits from carcinoma of lung and prostate, hæmangioblastoma of the cerebellum and hepatoma.

The polycythæmia regresses if the diseased kidney is removed, but may relapse if secondary deposits subsequently appear. It is not accompanied by splenomegaly, nor are the white cell or platelet counts raised as in polycythæmia rubra vera.

A raised plasma erythropoietin level can be detected in these cases of renal polycythæmia, which falls to normal after nephrectomy. It has been suggested that the stimulus to this increased production of erythropoietin is anoxia within the diseased kidney, but the exact mechanism of this process and why it should be a relatively rare accompaniment of gross renal pathology remain to be elucidated.

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Cystadenoma of the Liver

Bernard Williams FRCS

Mrs B, aged 64 when first seen in May 1951.

History: Right-sided abdominal pain and tenderness had been present for two weeks. The onset had been sudden and was unaccompanied by vomiting or digestive upset.

On examination: A healthy-looking woman of average build, apyrexial and not jaundiced. The right upper quadrant of the abdomen was occupied by a cystic tender mass which moved on respiration.

Operation (9.5.51): Right paramedian incision. A large cystic tumour was found growing from the undersurface of the right lobe of the liver. It was removed without undue difficulty, leaving a raw, oozing surface, in the centre of which was a thin-walled channel exuding bile. Apart from this, no direct communication with the intra- or extra-hepatic biliary system was found. A flap of peritoneum covering the tumour was used to cover the raw area. The gall-bladder contained a cholesterol solitaire, 2 cm in diameter, and was removed. The common bile duct was normal. A tube drain was placed down to the tumour bed through a stab wound.

Progress: Recovery was uneventful and bile leakage slight. The patient was last seen in June 1959, when she appeared to be in good health.

Pathology (Dr R D Clay): The specimen is that of an ovoid multilocular cyst, 21 × 17 cm, weighing 760 g. The contents of the loculi vary from clear mucinous fluid to brownish turbid material containing cholesterol crystals. Some of the smaller loculi contain soft papillary ingrowths arising from their walls. Section shows the capsule and septa to be composed of relatively acellular collagenous connective tissue. The loculi are lined by columnar mucus-secreting epithelium which, in the adenomatous areas, is thrown into complex folds supported by a scanty vascular stroma.

Discussion

Ewing (1941) states that cystic adenoma of the bile ducts is rare and that many of the recorded cases were only doubtfully neoplastic; he recognizes only 4 genuine cases from the literature, of which only one (Keen 1892) was solitary, multilocular and clearly adenomatous.

Warvi (1944) records a single case of bile cystadenoma.

Edmondson (1958) advises that the term cystadenoma should be confined to the multilocular cystic tumours lined with columnar epithelium and having a dense cellular stroma. He has personally studied a single case. Cystadenomata are to be distinguished from various forms of solitary and polycystic disease of the liver. The latter are usually unilocular and the fluid is not likely to be grossly mucinous. The loculi in cystadenomata have a tall columnar epithelium, papillary infoldings and a dense cellular type of stroma, features that are not at all characteristic of the other forms of cystic disease. From a review of the reported cases of solitary or localized cystic disease of the liver, it is difficult to decide which of them are truly cystadenomata. The structure of these tumours, which occur predominantly in women, is reminiscent of cystadenomata of the pancreas but none has so far been reported as becoming malignant, a complication sometimes noted in cystadenomata of the pancreas.

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A Solitary Simple Cyst of the Stomach

John W Bradbeer FRCS (for A M Desmond FRCS)

M M N, male, aged 23.

This patient, an Egyptian, was recently in hospital in Cairo with amœbic dysentery. Apart from the bowel symptoms, for two years he had experienced epigastric pain after meals with nausea, but no vomiting, heartburn, dysphagia, or hæmatemesis. The pain did not wake him at night. Clinically, there were no abnormal physical signs.

Investigations: Plain X-ray of the abdomen showed a large soft-tissue shadow, probably in the stomach. Barium meal showed the presence of a large rounded filling defect in the fundus, near the cardio-œsophageal junction. Gastroscopy revealed a submucosal tumour arising from the fundus. The mucosa over the tumour was normal. A provisional diagnosis of leiomyoma was made.

Operation: When the stomach was mobilized the tumour was palpated and found to be soft. It was therefore thought that the diagnosis of sarcoma

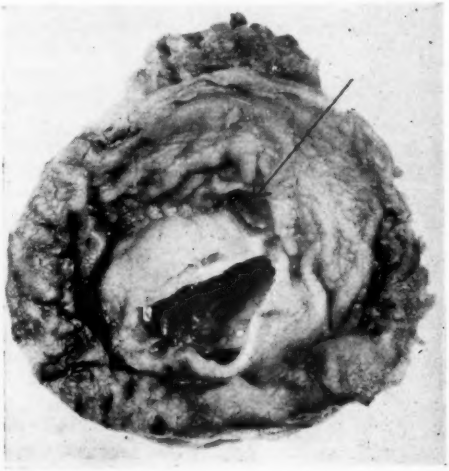

Fig 1 *Œsophageal opening shown by arrow*

was more likely than leiomyoma. Accordingly an upper partial gastrectomy with œsophagogastrostomy was carried out.

Macroscopic examination: A cyst, 7 cm in diameter, covered by normal gastric mucosa, lay in the submucous layer of the gastric wall. The lining was smooth (Fig 1).

Microscopic examination: A simple cyst over which lay gastric mucosa. The cyst was lined by connective tissue in which there was a mild inflammatory infiltrate. No specific pathology was seen.

Discussion

Pathology: Gastric cysts are uncommon, accounting for a very small percentage of all benign gastric tumours, which themselves comprise only 1·5% of gastric resections. Eusterman & Balfour (1935) recorded five cysts of the stomach in 4,000 gastric resections.

The differential diagnosis in this case would appear to lie between an enterogenous and a simple cyst. Fifteen cases of enterogenous cyst have been recorded in the last thirty years. Two of these duplications of the stomach were included by Ladd & Gross (1947) in their series of 68 patients with alimentary tract duplication. This cyst is not a duplication because it is thin walled, has no muscle coat, is not lined by epithelium, and can be separated from the stomach. By exclusion, therefore, it must be a simple cyst, the origin of which is unknown. The only other simple cysts of the stomach that I can find reported during the last thirty years are the two recorded by Eusterman & Balfour.

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Carcinoma of Colon Following Transplantation of the Ureters, and at the Site of the Transplantation

Arnold S Aldis FRCS

The patient, a female, first presented at the age of 18 in June 1943 with complete exstrophy of the bladder, which was treated by bilateral transplantation of the ureters into the pelvic colon, with excision of the extroverted bladder and plastic repair of the perineum. The patient remained well following this procedure and in 1955 was delivered of a male child by Cæsarean section. Immediately following delivery she had a severe attack of left-sided pyelonephritis, and intravenous pyelography carried out when the attack had subsided showed a very poor function with dilated ureter and pelvis on the left side. She had a further attack of left-sided pyelonephritis in the following year, and in December 1958 was readmitted with acute on chronic large intestine obstruction which proved to be due to a scirrhous carcinoma of the pelvic colon just at the point of implantation of the left ureter which was grossly dilated and completely obstructed. Following a preliminary transverse colostomy the carcinoma of the colon was excised and the right ureter was reimplanted in the colon; the left ureter being ligated. The patient remained well after this for a year and was then operated on in Bournemouth for acute intestinal obstruction which was found to be due to adhesions from multiple peritoneal metastases. She ultimately died in August 1960.

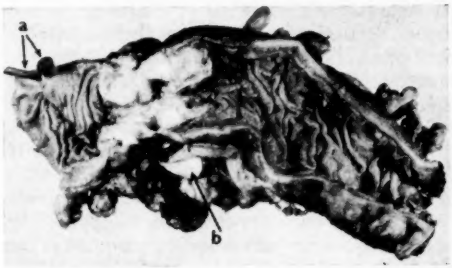


Fig 1 *Specimen of pelvic colon, showing* (a) *glass rod in right ureter with false polyp at the orifice,* (b) *carcinoma of colon extending into the dilated and obstructed termination of the left ureter*

The specimen shows the resected pelvic colon with the carcinoma surrounding the lumen and protruding as a cone-shaped papilla of growth into the grossly dilated lower end of the left ureter. The lower end of the right ureter is seen as a papilla or false polyp projecting about a centimetre into the lumen of the pelvic colon (Fig 1).

It seems likely from the history that the growth must have started at or very near the point where the left ureter had projected into the colon and it is suggested that there may be a causal relation between the transplantation of the ureter and the subsequent development of the carcinoma of the colon, for the following reasons: (1) The chance of a female patient developing a carcinoma of the pelvic colon at the age of 30 in the general population is very small indeed – about 1 in 100,000 (calculated from published figures). (2) The incidence of carcinoma of the colon on pre-existing polyps, both true and false, is well recognized and the time relations in this patient are of the order which is known to occur in the transformation of a benign pseudo-polyp into a carcinoma. (3) The lower end of the right ureter is projecting into the colon as an obvious false polyp, and a polyp furthermore which is rather firmer than the sur-

rounding bowel wall and with an abnormally adherent mucosa, both of which facts would render it more liable to repeated trauma.

Mr P T Savage reported that in the Whittington Hospital museum there was a specimen from a case similar to that reported by Mr Aldis, of carcinoma at the site of a ureteric transplant into the colon.

Amœboma of the Colon

R A Sellwood FRCS (for R H Franklin FRCS)

M J, male (Pakistani), aged 56.

History: 1958: Presented in Pakistan with diarrhœa, anæmia and a right-sided abdominal mass. At laparotomy a diagnosis of carcinoma of the hepatic flexure was made and right hemicolectomy performed. The specimen was not submitted for histology, but the patient was told that he had carcinoma of the large bowel. The operation was followed by relief of all symptoms.

May 1960: The patient was seen by Mr R H Franklin because he noticed another similar mass in the right side of the abdomen. He was in good health, had a good appetite and was not losing weight. He had no pain beyond discomfort at the site of the lump. There was no history of constipation or diarrhœa or of the passage of blood or slime per rectum.

Past history: Bacillary dysentery many years ago which responded to treatment. No history of amœbic dysentery.

On examination: Intelligent, well-built, well-nourished man. Mucous membranes good colour. No adenopathy. No finger clubbing. Abdomen not distended. Liver and spleen not palpable. Smooth, firm, spherical mass, about 10 cm in diameter, to the right of the umbilicus. It was slightly tender, mobile, and moved on respiration. Rectal examination normal. X-ray chest normal. A diagnosis of locally recurrent carcinoma of the colon was made.

Laparotomy (12.5.60): Right paramedian incision. A right hemicolectomy, with end-to-end anastomosis, had been performed previously and there was a large mass, thought to be typical of a recurrent neoplasm, involving the site of the previous anastomosis and invading the root of the mesentery. The liver was free of secondary deposits and there was no evidence of metastatic spread within the abdomen. The tumour was mobilized with difficulty and resected, an end-to-end ileo-colic anastomosis being performed.

Following operation the patient convalesced normally.

Pathology: Macroscopic: The specimen consisted of approximately 30 cm of bowel twisted into a mass. Approximately 20 cm were small bowel and 10 cm large bowel joined by a well-healed anastomosis. Around the area of anastomosis and extending for about 7 cm was a gross, whitish thickening of the wall of the colon, the thickness of the wall being 3–4 cm, involving all coats but mainly the serosal surface. In this area was a cavity external to the intestine with a thick wall which constituted the mass around which the bowel was twisted. Near the opening to the cavity the mucosa was ulcerated and the wall was hard, dense and white.

Microscopic: A widespread chronic inflammatory process was seen in which plasma cells predominated in the cellular infiltrate both in intact mucosa and in the granulation tissue covering ulcerated areas. Eosinophils, lymphocytes and macrophages were also numerous. The thickening of the bowel wall was fibroblastic and collagenous. Both vegetative forms and cysts of *Entamœba histolytica* were seen in the areas of necrosis.

Conclusion: This is an amœboma and there is no evidence of malignancy.

Mr H R I Wolfe showed slides demonstrating the rapid response of an amœboma of the cæcum and of cutaneous amœbiasis to anti-amœbic treatment.

Duplication of the Small Intestine

H Gordon Ungley MD FRCS

A boy aged 8 months with a history of melæna for two days. Hæmoglobin 27%. No abnormal findings on physical examination or after barium meal and follow-through. At operation duplicated ileum found 3 ft in length ending about 6 ft from the ileocæcal valve. Proximally the duplicated portion ended blindly; distally it tailed off into a narrow tube which passed towards the root of the mesentery. It was resected and end-to-end anastomosis performed. Recovery.

Specimen shows gastric mucosa in the duplicated gut and two ulcers one-third inch across (the source of the bleeding) in the adjacent ileum.

Squamous Cell Carcinoma of the Lung and Squamous Cell Carcinoma of the Kidney

L N Allen FRCS (for D R Davies FRCS)

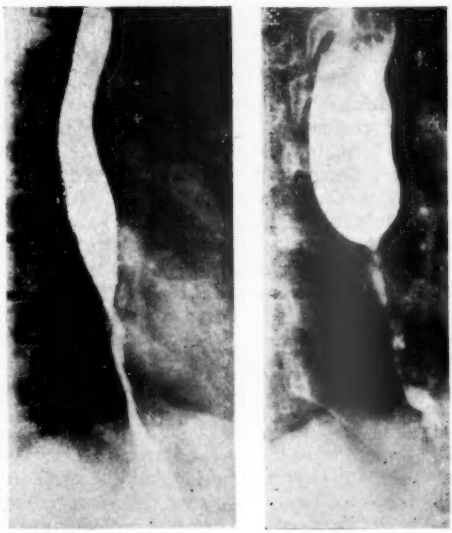
The patient had a primary squamous cell carcinoma of the lung excised in February 1960 and a primary squamous carcinoma of the kidney in June 1960. The interest lay in there being two primaries and the possibility of the carcinoma of the kidney being a secondary from the carcinoma of the lung presenting as a primary.

Pathological Changes in a Jejunal Graft used for Œsophageal Reconstruction

Donald Barlow MS FRCS

G F, female, aged 13.

History: Hæmatemesis necessitating blood transfusion when 2 days old but breast-fed without difficulty till 6 months. Subsequently, progressive dysphagia and regurgitation. At age of 10 years, stricture with ulceration demonstrated at 29 cm



A B

Fig 1 A, *original stricture.* B, *stricture in the jejunal graft*

(Fig 1A). Dilatations carried out at progressively shorter intervals. At age 13, child wasted and ill, and operation decided on.

Operation: Resection of stricture together with hiatus hernia. Jejunal graft 8 in. long implanted between stump of œsophagus above and stomach below – on pedicle of a single artery and vein. Graft extended to stomach which was then entirely below diaphragm and hiatus repaired by suturing together limbs of right crus and suturing lower end of graft to under side of diaphragm.

The preparation of this graft on its vascular pedicle was uneventful and no clamps were used. Jejunal continuity was restored by end-to-end anastomosis. The free length of jejunum was threaded up through a prepared hole in the mesocolon and lesser omentum and was anastomosed to the œsophageal stump. When this anastomosis had been completed, it was noted that the graft was blue and found that this was due to inadvertent rotation through 180 degrees of the graft on its single artery and vein. The anastomosis was undone, the rotation corrected, and top and bottom anastomoses completed. The period of graft cyanosis was less than 15 minutes. After untwisting, the gut was pink and healthy and its artery and branches pulsated. Healing was by first intention and the patient left hospital in two weeks.

Immediately following operation swallowing was almost normal, but within a month dysphagia recurred and progressed. Further X-rays, confirmed by œsophagoscopy, showed a stricture of the whole length of the graft (Fig 1B). Further operation was therefore decided on.

2nd operation: Resection with great difficulty of whole graft. Stomach brought up and joined to stump œsophagus. The jejunal graft macroscopically looked typical of Crohn's disease. Its walls were ¼ to ½ in. thick and the lumen was ulcerated throughout its length. The graft was embedded in enlarged and inflamed mediastinal glands and fibrous tissue.

Microscopically all lining mucosa of graft had vanished. Submucosa of graft was replaced by granulation tissue but without the focal patchy accumulations of lymphocytes seen in some cases of Crohn's disease.

There were no sarcoid-like changes consisting of histiocytes and giant cells present although scattered solitary giant cells were seen here and there. The mediastinal lymph nodes showed inflammatory changes but no histiocytes or giant cells.

A small leak developed at the œsophagogastric anastomosis on the tenth day with the formation of a localized mediastinal abscess, and the patient died suddenly on the fourteenth day from aspiration of vomited fluid.

Post-mortem: Confirmed the above findings. Otherwise the whole intestine, including the jejuno-jejunal anastomosis from which the graft was taken, was normal and there were no enlarged mesenteric glands.

Discussion: The changes in this jejunal graft were macroscopically those of Crohn's disease. Microscopically a typical case of Crohn's disease shows loss of the mucosa from ulceration, and œdematous granulation tissue replacing the normal structures of the bowel wall. By no means all show the classical lymphocytic accumulations nor the sarcoid-like areas with giant cells. In the present case, lymphocytes and sarcoid changes were not

present but the lesion was otherwise indistinguishable from regional ileitis.

This would appear to be the first time that Crohn-like changes have been reported in a jejunal graft, and the possibility arises that these changes were due to the temporary interference with the graft's blood supply. Other writers (Chiene 1869, Hawkins 1957) have drawn attention to similar lesions with jejunal stenosis from mesenteric artery occlusion, and in 1947 Spellberg & Ochsner confirmed what had already been recorded earlier, that similar lesions might result from non-penetrating injury to the small intestine.

This case appears to provide further evidence in support of a relation between vascular interference and intestinal granuloma.

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The following specimens were also shown:

(1) Suppurative Thyroiditis Presenting as Carcinoma of the Thyroid

(2) Hæmorrhage into an Adenoma of the Thyroid
Mr R V Cooke

Sturge-Weber Syndrome
Mr Donald Barlow

Gastrocolic Fistula due to Recurrent Carcinoma of the Colon
Mr P T Savage

(1) Sarcoma of the Ascending Colon
(2) Carcinoma of the Rectum Associated with Basal Cell Carcinoma of the Peri-anal Region
Mr M Ward (for Mr Clive Butler)

Leiomyosarcoma of the Small Intestine
Mr J I Burn (for Mr R H Franklin)

Extensive Cavernous Hæmangioma Involving the Right Upper Chest and Right Arm
Mr K Halstead Smith (for Mr R O Lee)

Pulmonary Actinomycosis
Mr R H P Oliver (for Mr H R I Wolfe)

Book reviews

Drugs of Choice 1960–1961
edited by Walter Modell MD
pp 958 illustrated 101s 6d
St. Louis: The C V Mosby Company
London: Henry Kimpton 1960

Drugs of Choice 1958–59 has been followed by a 1960–61 volume, a tribute to the industry and enthusiasm of its editors and contributors and their developing assessments of drugs both old and new. The natural history of the modern drug moves at a much faster pace than that of its predecessors and as a result publications of this nature have a real function in summarizing expert opinion as to the best therapeutic procedures. There are too many useful drugs available for any individual to hope to have adequate personal experience with all. The book has been expanded to include such subjects as sedatives and tranquillizers in general practice, anorexic agents, local antiseptics, and physical and chemical considerations in the choice of drugs. The book constitutes a collaborative textbook of clinical therapeutics expounding American thinking on this subject. Although based on drugs available in the United States, most of its lessons can be applied here in relation to both new and old drugs when equivalent preparations are available in this country. There is a useful drug index giving official and trade names. The references are practically all in English, mainly to American literature. The great majority of the advances in therapeutics are included and reported on, due emphasis being given as to their respective advantages and disadvantages.

St Peter's Hospital for Stone
edited by Clifford Morson OBE FRCS
pp viii+64 illustrated 21s
Edinburgh & London: E & S Livingstone Ltd 1960

Mr Clifford Morson has produced a book which befits the occasion of the centenary of St Peter's Hospital for Stone.

Many books on the history of medicine stand dustbound on the shelves of public libraries; too few grace the book-cases of the doctor. This book should not be relegated to darkened holes for it traces in a simple, interesting and most readable manner the development of the Hospital. The struggle for existence of this renowned specialized Hospital was waged against lay and medical opinion. The arrival of an anonymous benefactor on the doorstep of the Hospital rewarded this struggle and gave its Board the means whereby it could establish itself and finally become a centre for urological teaching and research. The surgeons who worked within its portals are ably portrayed and give an added interest to a book which is a most readable record of St Peter's Hospital.

Lectures on Hæmatology
edited by F G J Hayhoe MA MD MRCP
pp ix+247 illustrated 80s
Cambridge: The University Press 1960

This volume presents thirteen lectures delivered during a Symposium on Hæmatology held at Cambridge in December 1959, under the auspices of the University Postgraduate Medical School. It was designed to provide a 'refresher' survey of current knowledge in a rapidly expanding discipline and was directed to an audience of medical consultants and senior colleagues having hæmatology as one of their major clinical or laboratory interests. Whilst making no claim to present new or unpublished observations, this collection of papers provides a useful and, on the whole, easily readable source of both practical and theoretical up-to-date information. The specialist fully occupied in this subject should be conversant with the topics discussed and, as these will certainly require modification, and even revision, within a short time, he may not feel justified in paying a rather high price for a book which will soon be out of date. Its value is more likely to be appreciated by the clinical pathologist and general physician who has other commitments yet must keep abreast of advances in hæmatological diagnosis and treatment.

Hospital Infection. Causes and Prevention
by R E O Williams MD MRCP, R Blowers MD, L P Garrod MD FRCP and R A Shooter MD
pp viii+307 illustrated 35s
London: Lloyd-Luke (Medical Books) Ltd 1960

Recent years have seen a spate of conflicting publications on hospital infection, its spread, its incidence and its control. This slim and readable book, prepared by a team of four distinguished bacteriologists, who are acknowledged authorities in this field, comes at an opportune moment. The authors have produced an admirable review of the whole field of hospital infections.

The book is in two sections. The first surveys the mode of spread of many different hospital infections and here, not unnaturally, the staphylococcus receives special attention. The second

deals with prevention in all its aspects, including design of wards and theatres, methods of sterilization, and nursing and surgical techniques. There is an interesting contribution on the method of investigating an outbreak of hospital sepsis.

Since it deals with a subject whose ramifications are so extensive, there is little doubt that the appeal of this important book will be wide.

Current Therapy – 1960. Latest Approved Methods of Treatment for the Practising Physician
edited by Howard F Conn MD
pp xxxii+808 84s
Philadelphia & London:
W B Saunders Company Ltd 1960
This twelfth annual edition is a worthy successor to those of previous years. A careful reading of the descriptions of modern forms of treatment relating to many different medical conditions shows how carefully the volume has been brought up to date. The editor and his twelve contributors can be congratulated on the publication of yet another valuable contribution to modern treatment. It will be helpful to any physician practising internal medicine.

The Dyslipidoses
by Raúl Fleischmajer MD
pp xvi+509 illustrated £6 8s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960
The dyslipidoses is the author's name for the disorders of lipid metabolism. Dr Sulzberger, in the foreword, points out the great importance of the contributions of dermatologists to various aspects of general medicine and rightly remarks how suitable it is that a dermatologist should write a monograph on this borderland subject. The various forms of xanthoma, hyperlipæmia, and hypercholesterolæmia are the most obvious subjects treated. The others are myxœdema, diabetes mellitus, glycogen storage disease, nephrotic syndrome, pancreatitis, Gaucher's disease, Niemann-Pick disease, amaurotic family idiocy, gargoylism, histiocytosis-X, hyalinosis cutis et mucosæ (lipoid proteinosis), and extracellular cholesterosis. There is a particularly good chapter on nævoxanthoendothelioma for which, unfortunately, yet another new name is proposed. Not only are the essential historical facts stated about each of the disorders, but, as much too rarely happens, the references to the original papers are given. Each chapter gives a full account of one disorder with useful case histories, many excellent illustrations and well-selected bibliographies. The classification used is modified from the well-known one proposed by Thannhauser and Magendantz. The volume is admirably produced and has a good index. This admirable book is a necessity for all physicians interested in metabolic diseases and is recommended also to dermatologists.

Behaviour Therapy and the Neuroses
edited by H J Eysenck PhD
pp xi+479 illustrated 63s
Oxford, &c: Pergamon Press 1960
Methods of treatment discussed in this useful book include psychotherapy by reciprocal inhibition (Wolpe), systematic desensitization, negative practice, especially in the treatment of tics and certain stammers, aversion therapy, deconditioning treatment of writer's cramp, conditioning treatment of nocturnal enuresis and the treatment of stammering by 'shadowing'.

The claims made for these methods are modest and Eysenck's suggestion 'that a good case can be made out, both on the theoretical and the empirical level, for the proposition that behaviour therapy is an effective, relatively quick, and probably lasting cure of some neurotic disorders' seems justified.

It seems a pity that psychoanalysis is, as one would expect, treated so contemptuously ('unsupported assumptions and theories . . . mumpsimus beliefs . . .') but this should not obscure the fact that deductions from experimentally grounded Learning Theory have led to apparently successful methods of treatment for a variety of neurotic conditions, including several which respond badly to any other approach.

The book is well produced and has good author and subject indices.

Obstetrical and Gynæcological Pathology for Postgraduate Students
by R E Rewell MD MRCP
pp xii+435 illustrated 50s
Edinburgh & London: E & S Livingstone Ltd 1960
This book covers the whole field of gynæcological and obstetrical pathology, including vaginal cytology, infertility, various pregnancy complications (as pre-eclampsia, anæmia, and clotting defects), Rh disease, and perinatal mortality generally. This covers a wider field than the well-known book by Novak & Novak (*c.* 650 pages), and is directed to a different public. It is meant for the gynæcologist, whether for passing the MRCOG, getting a general theoretical background, or occasionally understanding his own sections.

Several criticisms can be made, mostly of detail. The book is rather long for its purpose, and could well be condensed in the next edition, for its treatment of many matters is necessarily sketchy. Some of the opinions are highly individual and need further documentation: few will agree with the account of the metaplastic vagaries of granulosal epithelium, or with the statement that follicle

hæmatomas are the commonest form of chocolate cyst. Some of the photographs are poor, and would convey little to anyone unacquainted with the condition depicted. The obstetrical part is probably the best.

This being said, the book can be recommended to those to whom it is addressed. It has no exact equivalent in English, is perfectly readable, and its idiosyncrasies would be unlikely (if retailed) to antagonize an MRCOG examiner. The author has had some special experience of his subject in India, notably in relation to uterine carcinoma.

The Pharmacology of Anesthetic Drugs: A Syllabus for Students and Clinicians
by John Adriani MD
4th ed pp xvi+232 illustrated 88s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

This is the 4th edition of a book which first appeared in 1940. It is certainly a formidable task to give a full account of the pharmacology of the ever-increasing number of anæsthetic agents and drugs used in conjunction with them. The author limits himself to fundamentals, using tables and diagrams to provide a wealth of easily available information.

A few points of criticism – the nomenclature of the drugs is very haphazard and sometimes confusing, and there are some inaccuracies, such as the classification of quinine and mephenesin as curare-like muscle relaxants.

However, by and large this is a most valuable book for anæsthetists, pharmacologists and others who want to get the facts about anæsthetic drugs.

The Tonsils and Adenoids in Childhood
by Donald F Proctor MD
pp xi+70 illustrated 60s
Pediatric Surgical Monograph Series
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

The most refreshing aspect of this new comprehensive monograph is the candour with which the author approaches the subject. The tone is set on the opening page by a frank discussion of the mortality rate, quoted as 300 deaths a year in 2,000,000 operations in the United States. Since the percentage incidence approximates to that in the United Kingdom, the author's contentions have strict relevance to British readers.

The general thesis is one with which the reviewer strongly agrees, namely that any operation is as major as the complications commonly encountered during or after its performance. The peri- and post-operative complications of tonsillectomy and adenoidectomy include severe hæmorrhage and respiratory obstruction, either of which can prove fatal. It is in the avoidance and improved management of these complications and in strict insistence on a high standard of anæsthetic administration that the serious reproach of the mortality rate is to be removed.

Some divergence of view on detail is inevitable. For example, radiotherapy for recurrent adenoids is advocated before the point is reached where growth requires secondary adenoidectomy. Most British authorities favour surgical re-removal wherever possible and radiotherapy only where the case is desperate on account of unrelieved deafness. Tests of hearing are inadequately presented for the successful assessment of deaf children, suggesting some unawareness of the depth of the problem. But with these, and a few other reservations, the monograph is wholly recommended as a valuable contribution towards an improved standard of practice in this still controversial field.

The Chemistry of Lipids in Health and Disease
by H K King MA PhD FRIC
American Lecture Series No 381
pp vii+104 illustrated 30s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960

This small monograph is designed primarily for physicians and students who have insufficient basic knowledge to understand the complex problems of lipid biochemistry. The author presents in reasonably simple terms the chemical structure of the lipids, the mechanisms involved in their absorption and oxidative breakdown and the principal stages in their biosynthesis within the body. Throughout these sections, which make up three-quarters of the book, emphasis is given to the biological application and significance of these aspects of lipid biochemistry. This biological approach is a merit of this book which also includes a valuable account of dietary lipids. Perspective occasionally goes awry; for example, considerable prominence is given to 'essential' fatty acids, but our lack of knowledge of their importance, if any, in human metabolism receives insufficient critical comment. Nor does the author give consideration to the lipid composition of arterial wall in his rather sketchy chapter on lipids and atherosclerosis.

This monograph should appeal and can be strongly recommended to those physicians who want to deepen their knowledge of this complex field without spending too much time doing so. Although it might be improved by a more factual and critical chapter on the relation of lipids to atherosclerosis, Dr King's final comment bears repetition: 'All responsible participants in atherosclerosis controversies agree that none of the

evidence yet available would justify advising the public to make radical changes in its dietary habits.'

A History of Psychiatry
by Jerome M Schneck AB MD
pp ix+196 illustrated 44s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960
This compact history of psychiatry is primarily intended for students, undergraduate and post-graduate. The earlier chapters are a fair summary of the history of medicine from the dawn of mankind until the Renaissance, for it is only after this time that the real beginnings can be found of the scientific approach to the study of the mind.

There is a great deal of information packed into this volume and there are selected yet adequate references. There are accounts of Caelius Aurelianus who in the latter days of Rome removed shackles from the mentally sick and sought their co-operation by providing exercise and entertainment, of Juan Luis Vives 'the Father of Modern Psychology', and Johann Weyer, the astute sixteenth century psychiatrist who in so many respects was much ahead of his time, although he disappoints his admirers by having so precisely enumerated the demons (his estimate was 7,490,127) and the princes whom he alleged controlled them. There is a description, too, of the early Spanish asylums, notably those at Valencia, Seville and Zaragosa, and of their likely influence on Philippe Pinel.

The growth of psychiatry out of witchcraft and the evolution of the sorcerer and the mesmerist into the present-day psychiatrist constitute one of the most romantic chapters of medical history. Some will find this account too condensed to make enjoyable reading but the student of psychiatry wishing to acquire some knowledge of the history of his subject will find in this volume what he requires.

Clinical Pharmacology
by D R Laurence MD MRCP and R Moulton MB
pp viii+490 32s
London: J & A Churchill Ltd 1960

Dillings' Clinical Pharmacology
revised by
Stanley Alstead CBE MD FRFPS FRCP FRCPED FRSED
20th ed pp xv+860 30s
London: Cassell 1960
These two textbooks of clinical pharmacology are similar in size, price, purpose and, to some extent, in content. One is new, the other is the twentieth edition of a well-known text. Both aim to provide an account of that scientific basis for the use of drugs which is generally held to be desirable. The concept of what is a scientific basis differs. To this reviewer, the basis of science itself is controlled experiment, and a controlled experiment in therapeutics consists of comparing a drug with a dummy or alternative medicament. Laurence and Moulton start in Chapter I with a discussion of the effects of dummies, and do not begin to deal with specific drugs until they have dealt with therapeutic trials. In Dilling, on the other hand, science is on the whole taken as what happens in a laboratory, and very little attention is paid to scientific thinking in the actual use of drugs. There is plenty of sound clinical advice, but the constant urge for assessment and evaluation is lacking. The work starts with a chapter on pharmacopœias and prescribing, and clinical trials are mentioned in the final chapter and then only sketchily. It is perhaps a corollary of these different approaches that Laurence and Moulton document their work with a steady supply of references on debatable points, whereas in Dilling there is only a very limited guide to further reading and no support is cited for either important or debatable statements. In spite of a considerably shorter text, Laurence and Moulton are about as comprehensive as Dilling, and it is clear that the new authors have written an exceptionally good small textbook on applied pharmacology. Dilling is unfortunately not in the same class, though no doubt some will prefer its more leisurely style and the distinction of its venerable history.

French's Index of Differential Diagnosis
edited by Arthur H Douthwaite MD FRCP
8th ed pp xii+1111 illustrated 126s
Bristol: John Wright & Sons Ltd 1960
The first edition of 'French' appeared almost fifty years ago. The author's original aim, to catalogue all symptoms and signs seen in clinical medicine, has been maintained by Dr Douthwaite and Sir Adolphe Abrahams; to achieve it is probably impossible, but in the attempt the 20 authors have contributed a million words, 750 illustrations (some distinctly old fashioned) and 150 pages of index. The effort is massive. Whether it was worth making is another matter.

Outline of Fractures Including Joint Injuries
by John Crawford Adams MD FRCS
3rd ed pp vii+268 illustrated 27s 6d
Edinburgh & London: E & S Livingstone Ltd 1960
Once again Mr Crawford Adams' lucid and informative book appears as a new edition. What revisions of text and alterations of diagrams there are serve only to improve the excellence of the work which is now firmly established as one of the most reliable books upon which medical students, house officers and practitioners have come to depend.

Gynecological Urology
compiled and edited by
Abdel Fattah Youssef MB DS DGO MCh FICS
pp xvii+893 illustrated £9
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960
This new book covers its subject exhaustively in forty-two chapters contributed by thirty-two distinguished authors from many different countries. The editor, himself a contributor of note, is to be congratulated on assembling and marshalling such a galaxy of stars within its covers. Each chapter is an independent monograph, expressing the views and techniques of its author, and referring to alternative techniques. Here and there many different techniques are presented without critical evaluation, so that the reader is left to choose for himself which is most appropriate. This may be for some an advantage, while for others it detracts from the value of the book as a whole. The book is well produced and the standard of illustration, though variable, is generally high. The illustrations are numbered only in relation to the chapter in which they occur, so that, for example, Fig 6 appears many times, but always in different guise. Serial numbering throughout the whole book would have been more helpful. Again, the name of the author of each chapter could with advantage have appeared as the left-hand headline, and the subject as the right-hand headline, greatly increasing the value of the book for reference. The index is comprehensive and accurate, and the type clear.

These minor criticisms should not detract from the immense value of this book, which presents in great detail and with clarity every aspect of gynæcological urology in an authoritative way, and will undoubtedly become an important resident on every gynæcological bookshelf.

Clinical Medicine: The Modern Approach
by A E Clark-Kennedy MA MD FRCP and
C W Bartley MA DM MD MRCP
pp x+425 25s
London: Pitman Medical Publishing Co Ltd 1960
It is difficult to be sure for whom this book is intended. Parts of it, such as the chapter on The Patient & His Disease, will be of interest to the medical student early in his clinical course and to the student nurse. The chapter on the Dying Patient, which is excellent, will not have much meaning until later in his career. The chapter on Organic Disease is too elementary, one would hope, for a student who has spent two years studying physiology, biochemistry and pharmacology and is written in a style calculated to convince the student that on arrival at the hospital he has been mistakenly admitted to the children's ward. This is an honest attempt to present diseases as the interaction between genetic predisposition, age and environment in an individual but it fails to discuss these influences at more than a superficial level.

Clinical Bacteriology
by E Joan Stokes MB FRCP
2nd ed pp x+309 illustrated 30s
London: Edward Arnold (Publishers) Ltd 1960
'Clinical Bacteriology' was written for pathologists and their technicians, for clinicians who wished to know what help to expect from the laboratory, and for those who had to instruct nurses how to collect specimens from patients. The first edition was widely welcomed, and this second edition, five years later, should be as warmly received. Not everyone will agree with all Dr Joan Stokes' recommendations, but in a working manual this is to be expected. Even if other methods are preferred, this book provides an excellent background against which they can be judged.

The Transparency of the Cornea
edited by Sir Stewart Duke-Elder and E S Perkins
pp xii+268 illustrated 45s
Oxford: Blackwell Scientific Publications Ltd 1960
This symposium on corneal transparency was organized by the Council for International Organizations of Medical Sciences, and investigators were brought together from widely dispersed parts of the globe so that their specialized knowledge might be pooled, in the hope that fresh ideas would arise therefrom. The result is a fascinating and learned series of papers, all written about some facet of corneal transparency and all from a different angle. Anatomy, physiology, pathology, biochemistry, physics, surgery and histology, and other disciplines are represented, and the discussions as published give an uninhibited touch to the prepared papers. No epoch-making discoveries are recorded, nor would they be expected, but for an up-to-date account of the present understanding of the cornea and how it works, this record has no equal in medical literature.

Diabetes Mellitus
A Clinical and Pathological Study of 2,529 Cases
by E T Bell MD
pp viii+67 illustrated 30s
American Lecture Series No 410
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications Ltd 1960
This little book is based upon the study of a large number of necropsies on diabetics. It is written by a pathologist and, although it claims to be a clinical and pathological study, it is predominantly pathological. It would have been better to make this limitation clear in the title. A book,

however short, which does not mention insulin in the index cannot claim to be a clinical study of diabetes. Nor is a bibliography of 34 references adequate.

The price of this book is absurd. There are 8 figures and 61 pages of text, each of only 300 words, and there are serious typographical errors. As this lecture contains no original observations and is not a comprehensive account of present knowledge it is hard to see why it was published.

Mackie and McCartney's Handbook of Bacteriology
A Guide to the Laboratory Diagnosis and Control of Infection
edited by Robert Cruickshank MD FRCP DPH FRSE
10th ed pp xi+980 illustrated 40s
Edinburgh & London: E & S Livingstone Ltd 1960

Mackie and McCartney was first published in 1925 and in the course of nine editions it became the standard textbook for methods in bacteriological laboratories, used alike by technicians preparing for their examinations, and pathologists and technicians during the day's work. Professor Mackie died in 1955 and Dr McCartney has retired, and this new edition has been produced by Professor R Cruickshank and his colleagues in the Department of Bacteriology, Edinburgh University. It has been extensively rewritten, and is some 230 pages longer than the last edition. This extra length is partly accounted for by the inclusion of new material. Viruses claim eight chapters instead of one, a change which is justified by the considerable advances in virology and the recognition that the laboratory diagnosis of virus disease is becoming possible as a routine measure. Additional room, too, has been given to basic aspects of microbial infection, and this change is reflected in some of the sections where the bare facts have been supplemented by historical and theoretical details. There is no reason to doubt that this new edition will be as popular as its predecessors.

Anaerobic Bacteriology in Clinical Medicine
by A Trevor Willis PhD MB BS
pp xii+163+13 illustrated 30s
London: Butterworth & Co (Publishers) Ltd 1960

As the first to be entirely devoted to the subject of anaerobic bacteriology in clinical medicine, this book should be widely welcomed in clinical laboratories everywhere. Though the importance of anaerobic culture in diagnostic bacteriology is repeatedly stressed in the handbooks, trainees and technicians often fight shy of putting up anaerobic cultures because of the supposed difficulty of producing anaerobiosis. The first part of this book contains a lucid, well-illustrated account of all the well-tried methods of anaerobic culture, suitable for both large and small laboratories. There is also a chapter devoted to culture media in which a great variety of fluid and solid media are described and evaluated.

The second part of the book is concerned with the identification and characteristics of the pathogenic anaerobic organisms, describing the main features for the positive recognition of particular species. The third part is concerned with clinical infections and toxicology of the anaerobes. It is the size for ready reference, and should soon become a standard bench book.

Lymphocytes and Mast Cells
by Margaret A Kelsall BA MA PhD
and Edward D Crabb BA MA PhD
pp xvi+399 illustrated 64s
Baltimore: The Williams and Wilkins Company
London: Baillière, Tindall & Cox Ltd 1959

This substantial book deals with lymphocytes, plasmacytes and mast cells, their formation and the tissues in which they may be found, such as the thymus, spleen and bone-marrow. The last chapter is on inflammation and wound healing. The book is not easy to read; it is packed with references, some cited from abstracts, others ('histological citations') quoted from other papers, and many conflicting opinions and unorthodox statements are set down one after the other. Except for a set of 31 photomicrographs, mostly illustrating mast cells and lymphocytes, there are no illustrations.

The authors are biologists and this is clearly a handicap to them when they stray into medical fields. For instance, in a discussion on the effect of splenectomy on erythrocytes, this has led them to choose as an example of how the operation may influence disease in man its use as a means of therapy in pernicious anæmia, quoting a reference from the German literature dated 1929 which they had read in an abstract.

CORRIGENDUM

Symposium on Disseminated Sclerosis
January 1961 *Proceedings*, p. 9

Line 23 of Dr Acheson's contribution should read: 'the death rate from D.S. there was 0·76 per 100,000'

[The figure of 0·76 represents the average death rate during 1950–9 age-adjusted to the structure of the U.S. population in 1950. – E. D. A.]